SCIE DOI: 10.14744/scie.2025.69783
South. Clin. Ist. Euras. 2025;36(1):12-15

Original Article

Respiratory Evaluation in Patients Diagnosis of Biotinidase Deficiency

Mine Yüksel Kalyoncu,[1] Ece Öge Enver[2]

[1]Department of Pediatric Pulmonology, Kartal Dr Lutfi Kirdar City Hospital, Istanbul, Türkiye
[2]Department of Pediatric Metabolic Diseases, Kartal Dr. Lütfi Kırdar City Hospital, Istanbul, Türkiye

Submitted: 31.01.2025
Revised: 13.02.2025
Accepted: 13.02.2025

Correspondence: Mine Yüksel Kalyoncu,
Department of Pediatric Pulmonology, Kartal Dr Lutfi Kirdar City Hospital, Istanbul, Türkiye
E-mail: mineeyuksell@gmail.com

Keywords: Asthma; biotinidase deficiency; pulmonary function tests; respiratory function.

ABSTRACT

Objective: Biotinidase deficiency (BD) is a rare autosomal recessive metabolic disorder leading to neurological, dermatological, and, potentially, respiratory complications. While neurological and cutaneous manifestations of BD are well-documented, respiratory involvement remains less explored.This study aimed to evaluate respiratory function in patients diagnosed with BD, specifically assessing the presence of chronic respiratory symptoms and their potential relationship with BD.

Methods: We conducted a retrospective study of 13 patients with confirmed BD who presented with respiratory complaints at our pediatric pulmonology clinic. Clinical evaluations, pulmonary function tests (PFTs), and bronchodilator responsiveness were assessed. Statistical analyses were performed using SPSS 25.0.

Results: The median age of patients was 9 years (IQR: 9-13), with 61.5% being female. A total of 77% had parental consanguinity. Three patients (23.1%) exhibited obstructive patterns on PFTs, all of whom demonstrated significant bronchodilator responsiveness. These patients were treated with long-acting beta-agonists and inhaled corticosteroids, resulting in resolution of symptoms within three weeks. No significant correlation was observed between biotinidase enzyme activity and respiratory parameters.

Conclusion: The prevalence of reversible airway obstruction in BD patients closely aligns with the general population prevalence of asthma, suggesting that these findings may be coincidental rather than causally related to BD. Standard asthma therapy effectively alleviated symptoms, further supporting this interpretation. Future research with larger cohorts and long-term follow-up is warranted to clarify the respiratory implications of BD.

INTRODUCTION

Biotinidase deficiency (BD) is a rare autosomal recessive metabolic disorder characterized by the inability to recycle biotin, an essential vitamin B complex.[1] This condition, if left untreated, can lead to a wide range of clinical manifestations, including neurological, dermatological, and respiratory symptoms.[2] While neurological and cutaneous symptoms are well-documented, respiratory complications in BD patients are less frequently discussed in the literature, despite their potential severity and impact on patient outcomes.[2,3]

Respiratory problems associated with BD can manifest in various forms, including hyperventilation, laryngeal stridor, and apnea.[4] These symptoms can be particularly challenging to diagnose and manage, as they may be mistaken for other respiratory conditions or overlooked in the presence of more prominent neurological or dermatological manifestations.[5]

The incidence of BD is estimated to be approximately 1 in 60,000 newborns, with variations across different populations.[6] However, the true prevalence of respiratory complications within this patient group remains unclear, highlighting the need for further investigation and characterization of these symptoms.

Early diagnosis and treatment with biotin supplementation can prevent or reverse many of the clinical manifestations of BD, including respiratory symptoms.[3] However, the effectiveness of biotin treatment specifically for respiratory complications and the long-term respiratory outcomes in BD patients have not been extensively studied.

In general practice, cough stands out as the most common non-specific indicator of respiratory tract disorders. It presents in various forms and can be attributed to a wide array of causes. A chronic persistent cough is characterized as an annoying, non-productive cough that typically lasts for more than four weeks.[7] It is associated with normal chest x-ray findings and spirometry results, and lacks an evident or documented cause.[7]

The aim of this study is to evaluate patients presenting with chronic respiratory symptoms, specifically chronic cough and dyspnea, who have been diagnosed with BD at our center. Furthermore, we aim to determine whether these symptoms are direct manifestations of the disease or arise from independent comorbid conditions. Through this investigation, our research seeks to enhance the understanding of respiratory involvement in BD and contribute to the optimization of clinical management strategies for affected individuals.

MATERIALS AND METHODS

This retrospective study was conducted at our pediatric pulmonology department, evaluating patients diagnosed with BD who presented with respiratory complaints. The study protocol was approved by the institutional ethics committee (Protocol no:2025/010.99/12/3).

Patient Selection and Data Collection

We included all patients with confirmed BD who were referred to our pediatric pulmonology outpatient clinic with respiratory symptoms between February 2024 and January 2025. The diagnosis of BD was based on enzymatic testing showing biotinidase activity <30% of mean normal serum biotinidase activity.[2] Patients' medical records were reviewed to collect demographic data, clinical presentation, and laboratory findings.

Clinical Evaluation

All patients underwent a comprehensive physical examination focusing on respiratory signs and symptoms. The examination included assessment of respiratory rate, presence of dyspnea, wheezing, and other relevant findings. Oxygen saturation was measured using pulse oximetry (Masimo Radical-7, Masimo Corp., Irvine, CA, USA) with the patient at rest and breathing room air.[8]

Pulmonary Function Testing

Pulmonary function tests (PFTs) were performed on all patients who were able to cooperate (typically those over 5 years of age). We used a spirometer (MasterScreen PFT System, CareFusion, Hoechberg, Germany) to measure forced vital capacity (FVC), forced expiratory volume in one second (FEV1), and the FEV1/FVC ratio.[9] The best of three technically acceptable maneuvers was recorded, in accordance with American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines.[10]

To assess bronchodilator responsiveness, we administered 400 µg of salbutamol via a metered-dose inhaler with a spacer device. Spirometry was repeated 15 minutes after bronchodilator administration. A positive bronchodilator response was defined as an increase in FEV1 of ≥12% and ≥200 mL from baseline.[11]

Statistical Analysis

Statistical analysis was performed using SPSS version 25.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were presented as means ± standard deviations for continuous variables and percentages for categorical variables. Paired t-tests were used to compare pre- and post-bronchodilator PFT results. A p-value <0.05 was considered statistically significant.

RESULTS

A total of 13 patients with confirmed BD were enrolled in the study. The median age (25th-75th percentile) was 9 years (9-13 years) with 8 (61.5%) individuals being female. Two parent was diagnosed with BD, whereas three siblings had BD. Approximately 77% of patients exhibited parental consanguinity (Table 1).

The Newborn Screening Program (NBS) identified 84.7% of the total cases, while family screening accounted for 15.3%. None of these 11 patients diagnosed with NBS had active symptoms at the time of diagnosis. The remaining 2 patients had skin findings such as hair loss. Median biotinidase enzyme activity was 1,43 U/L (25-75p), 1,12-2,24) and median blood venous gas lactate 1,55 mmol/lt (25-75p, 1,42-2,17) (Table 1). There was no correlation between the enzyme activity and blood venous gas lactate level.

The patients' mean+std FVC was 83.3±12, FEV1 was 88.7±12.4 and FEV1/FVC was 105.8±9.4. Upon evaluation of their respiratory function, we found that three out of the 13 patients (23.1%) exhibited obstructive patterns on pulmonary function tests and two of these patients (66.6%) were male. These patients underwent further assessment to determine the reversibility of their airway obstruction. Reversibility testing was performed using salbutamol. All three patients with obstructive patterns demonstrated a positive response to the bronchodilator challenge (>%12).

Long-acting beta-agonist and inhaled steroid therapy was started in three children, and after one week of starting treatment, there was a decrease in the frequency of nighttime cough. The cough completely disappeared within week three of therapy. Children who responded to treatment had higher eosinophil counts in their blood com-

Table 1. Demographic data of the study group (n:13)

Age (years), median (25-75p)	9 (9-13)
Male, n (%)	5 (38.5)
Height (cm), (mean±std)	141.4±11.9
Weight (kg), (mean±std)	34.3±9.8
Boddy Mass Index (BMI), (mean±std)	16.8±2.6
Parental consanguinity, n (%)	10 (76.9)
Biotinidase enzyme activity, (U/L), median (25-75p)	1.43 (1.12-2.24)
Blood venous gas lactate (mmol/lt), median (25-75p)	1.55 (1.42-2.17)
Blood eosinophil count, n	210 (125-315)

U/L: Units per litre

pared with children who were not given treatment, but this difference was not statistically significant (p>0.05).

DISCUSSION

Our findings reveal some insights into the respiratory manifestations of this rare metabolic disorder. In cohort of 13 BD patients, lung function tests were consistent with asthma in three patients (23.1%). This prevalence is noteworthy as it closely aligns with the general population prevalence of asthma, which ranges from 1% to 18% in different countries.[12-14] Our results are more likely to be related to concurrent asthma rather than a direct consequence of BD. The slight variation in our findings may be attributed to differences in study populations, small sample size, and regional factors.

The similarity between our observed rate of reversible airway disease and the general prevalence of childhood asthma suggests that these findings are likely coincidental rather than causally related to BD. This interpretation is further supported by the fact that the respiratory abnormalities responded to standard asthma treatments, including bronchodilators and inhaled corticosteroids, which are not specific therapies for BD-related complications. [14] Furthermore, the observation that the patients' blood lactate levels are within normal parameters and they do not exhibit symptoms of BD indicates that the drug concentrations are adequate and diminishes the likelihood of complications.

It is important to note that while our study found no direct link between BD and reversible airway disease, previous research has reported various respiratory manifestations in BD patients, including hyperventilation, laryngeal stridor, and apnea.[15,16] However, these symptoms are generally attributed to neurological involvement rather than primary respiratory pathology.[17]

The age distribution and risk factors associated with asthma in the general pediatric population align with our observations in BD patients. For instance, the higher prevalence of asthma in boys compared to girls before puberty is a well-established pattern in childhood asthma epidemiology, and this trend was also evident in our cohort.[18]

Previous studies have reported that eosinophilic airway inflammation may play a role in the mechanism of nonspecific chronic cough.[7,19] Although our study did not specifically assess atopy, eosinophilia, or other known asthma risk factors, eosinophil counts were higher in BD patients with concomitant asthma in our cohort, which we believe may explain the observed respiratory patterns without directly implicating BD as a cause. Future research could benefit from a more detailed evaluation of asthma risk factors in BD patients to further elucidate this relationship.

It is worth noting that chronic respiratory diseases, including asthma, can coexist with various genetic and metabolic disorders without being directly caused by them.[20-22] The complex interplay between genetic predisposition and environmental factors in asthma development applies to children with BD as it does to the general population.

One limitation of our study is the relatively small sample size, which is not unexpected given the rarity of BD. Larger, multi-center studies would be beneficial to further elucidate any potential respiratory implications of BD. Additionally, long-term follow-up of BD patients could provide valuable insights into the natural history of respiratory function in this population. The slight variation in our findings may be attributed to differences in study populations, small sample size, and regional factors.

In conclusion, our study found that the prevalence of reversible airway disease in BD patients closely mirrors the general population prevalence of asthma. The positive response to bronchodilator therapy and standard asthma treatment in affected individuals further supports the interpretation that these findings are likely coincidental rather than causally related to BD. While respiratory evaluation remains an important aspect of comprehensive care for BD patients, our results suggest that reversible airway disease should not be considered a primary manifestation of BD. Future research should focus on larger cohorts and long-term outcomes to further clarify the respiratory health of individuals with BD.

Ethics Committee Approval

The study was approved by the Kartal Dr. Lutfi Kırdar City Hospital Ethics Committee (Date: 24.01.2025, Decision No: 2025/010.99/12/3).

Informed Consent

Retrospective study.

Peer-review

Externally peer-reviewed.

Authorship Contributions

Concept: M.Y.K.; Design: M.Y.K.; Supervision: M.Y.K.; Fundings: M.Y.K.; Materials: M.Y.K.; Data collection &/or processing: E.Ö.E.; Analysis and/or interpretation: E.Ö.E.; Literature search: M.Y.K.; Writing: M.Y.K.; Critical review: M.Y.K.

Conflict of Interest

None declared.

REFERENCES

1. Wolf B. Biotinidase deficiency: "If you have to have an inherited metabolic disease, this is the one to have". Genet Med 2012;14:565–75. [CrossRef]
2. 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;19:1–10. Erratum in: Genet Med 2018;20:282. Erratum in: Genet Med 2023;25:164–5. [CrossRef]
3. Procter M, Wolf B, Crockett DK, Mao R. The biotinidase gene variants registry: A paradigm public database. G3 (Bethesda) 2013;3:727–31. [CrossRef]
4. Bousounis DP, Camfield PR, Wolf B. Reversal of brain atrophy

with biotin treatment in biotinidase deficiency. Neuropediatrics 1993;24:214–7. [CrossRef]
5. Karaca M, Özgül RK, Ünal Ö, Yücel-Yılmaz D, Kılıç M, Hişmi B, et al. Detection of biotinidase gene mutations in Turkish patients ascertained by newborn and family screening. Eur J Pediatr 2015;174:1077–84. [CrossRef]
6. 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;12:464–70. [CrossRef]
7. Kopriva F, Sobolová L, Szotkowská J, Zápalka M. Treatment of chronic cough in children with montelukast, a leukotriene receptor antagonist. J Asthma 2004;41:715–20. [CrossRef]
8. Jubran A. Pulse oximetry. Crit Care 2015;19:272. [CrossRef]
9. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al; ATS/ERS Task Force. Standardisation of spirometry. Eur Respir J 2005;26:319–38. [CrossRef]
10. Graham BL, Steenbruggen I, Miller MR, Barjaktarevic IZ, Cooper BG, Hall GL, et al. Standardization of spirometry 2019 update. An official American Thoracic Society and European Respiratory Society Technical Statement. Am J Respir Crit Care Med 2019;200:e70–88. [CrossRef]
11. Pellegrino R, Viegi G, Brusasco V, Crapo RO, Burgos F, Casaburi R, et al. Interpretative strategies for lung function tests. Eur Respir J 2005;26:948–68. [CrossRef]
12. Yawn BP, Wollan P, Kurland M, Scanlon P. A longitudinal study of the prevalence of asthma in a community population of school-age children. J Pediatr 2002;140:576–81. [CrossRef]
13. Janahi IA, Bener A, Bush A. Prevalence of asthma among Qatari schoolchildren: International study of asthma and allergies in childhood, Qatar. Pediatr Pulmonol 2006;41:80–6. [CrossRef]
14. Alfonso J, Pérez S, Bou R, Amat A, Ruiz I, Mora A, et al. Asthma prevalence and risk factors in school children: The RESPIR longitudinal study. Allergol Immunopathol (Madr) 2020;48:223–31. [CrossRef]
15. Koohmanaee S, Zarkesh M, Tabrizi M, Hassanzadeh Rad A, Divshali S, Dalili S. Biotinidase deficiency in newborns as respiratory distress and tachypnea: A case report. Iran J Child Neurol 2015;9:58–60.
16. Canda E, Yazici H, Er E, Kose M, Basol G, Onay H, et al. Single center experience of biotinidase deficiency: 259 Patients and six novel mutations. J Pediatr Endocrinol Metab 2018;31:917–26. [CrossRef]
17. Yılmaz B, Ceylan AC, Gündüz M, Ünal Uzun Ö, Küçükcongar Yavaş A, Bilginer Gürbüz B, et al. Evaluation of clinical, laboratory, and molecular genetic features of patients with biotinidase deficiency. Eur J Pediatr 2024;183:1341–51. [CrossRef]
18. Fuseini H, Newcomb DC. Mechanisms driving gender differences in asthma. Curr Allergy Asthma Rep 2017;17:19. [CrossRef]
19. Kim YH, Jang YY, Jeong J, Chung HL. Increased serum eosinophilic cationic protein in children with nonspecific chronic cough. Clin Exp Pediatr 2023;66:455–7. [CrossRef]
20. Sgrazzutti L, Sansone F, Attanasi M, Di Pillo S, Chiarelli F. Coaggregation of asthma and type 1 diabetes in children: A narrative review. Int J Mol Sci 2021;22:5757. [CrossRef]
21. Cottrell L, Neal WA, Ice C, Perez MK, Piedimonte G. Metabolic abnormalities in children with asthma. Am J Respir Crit Care Med 2011;183:441–8. [CrossRef]
22. Grasemann H. Metabolic origins of childhood asthma. Mol Cell Pediatr 2015;2:6. [CrossRef]

Biyotinidaz Eksikliği Tanısı Olan Hastalarda Solunum Sistemi Değerlendirmesi

Amaç: Biyotinidaz eksikliği (BE), nadir görülen otozomal resesif bir metabolik hastalık olup nörolojik, dermatolojik ve nadiren respiratuvar komplikasyonlara yol açabilmektedir. BE'nin nörolojik ve kutanöz belirtileri iyi tanımlanmış olmasına rağmen, solunum sistemi üzerindeki etkileri yeterince araştırılmamıştır. Bu çalışmada, kronik solunumsal semptomları olan BE tanısı almış hastalarda respiratuvar değerlendirme yapılması ve bu semptomların BE ile olası ilişkisi değerlendirildi.

Gereç ve Yöntem: Çocuk göğüs hastalıkları polikliniğimize solunum şikayetleri ile başvuran ve BE tanılı 13 hasta retrospektif olarak incelendi. Hastalar klinik değerlendirme, solunum fonksiyon testleri (SFT) ve bronkodilatör yanıt açısından değerlendirildi. İstatistiksel analizler SPSS 25.0 kullanılarak gerçekleştirildi.

Bulgular: Hastaların medyan yaşı 9 yıl (IQR: 9-13) olup, %61.5'i kızdı. %77'sinde ebeveynler arası akrabalık öyküsü mevcuttu. Üç hastada (%23.1) obstrüktif solunum fonksiyon paternleri saptandı ve tümü bronkodilatörlere anlamlı yanıt gösterdi. Bu hastalara uzun etkili beta-agonist ve inhale kortikosteroid tedavisi başlandı; tedavinin ardından üç hafta içinde semptomlarda tamamen düzelme sağlandı. Biyotinidaz enzim aktivitesi ile solunum parametreleri arasında anlamlı bir korelasyon bulunmadı.

Sonuç: BE hastalarında saptanan reversibl hava yolu obstrüksiyonu, genel popülasyondaki astım prevalansı ile benzer oranlardadır. Bu durumun BE'ye özgü bir solunumsal belirti olmaktan çok, rastlantısal bir birliktelik olduğu düşünülmektedir. Standart astım tedavisi ile semptomların düzelmesi de bu yorumu desteklemektedir. BE'nin solunum sistemi üzerindeki uzun vadeli etkilerini netleştirmek için daha büyük hasta gruplarında ve uzun süreli takip çalışmaları gerekmektedir.

Anahtar Sözcükler: Astım; biyotinidaz eksikliği; solunum fonksiyonu; solunum fonksiyon testleri.