DERLEME / *REVIEW*

Biotinidase Deficiency as a Regional Problem and Solution Suggestions

Bölgesel Bir Sorun Olarak Biyotinidaz Eksikliği ve Çözüm Önerileri

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Abstract

Biotinidase enzyme is the enzyme that activates biotin, which is the cofactor of 4-carboxylase enzymes in our body. After its deficiency began to be treated in 1971, it was screened in the 1980 s. A local newborn study was conducted in our country under the leadership of the Istanbul Faculty of Medicine between 1991 and 2005, and the first data were obtained. As a result of this study, it was shown that biotinidase deficiency, which is known to occur in one in 60,000 people worldwide, is seen at a frequency of one in 11,000. Biotinidase newborn screening was added to the national screening program in our country in 2012, with a reported frequency of one in 5500. National screening data supported Istanbul University, revealing that the most common region was Northeastern Anatolia, with the provinces having the highest number of patients being Ardahan, Kars, and Iğdır. The number of centers that can perform metabolic follow-up of diagnosed patients in the region is insufficient. It was decided to write this article to highlight the need to establish a "Biotinidase Deficiency Research Institute" affiliated with Kafkas University in Kars, one of the provinces with the highest incidence of patients, to provide an on-site solution to the problem.

Key words: *biotinidase deficiency; newborn screening; hereditary deafness; hereditary blindness; demyelinating diseases; alopecia; sudden infant death syndrome; genetic diseases*

Özet

Biyotinidaz enzimi, vücudumuzda 4-karboksilaz enziminin kofaktörü olan biyotinin aktif hale getirilmesini sağlayan enzimdir. Eksikliği 1971'de tedavi edilmeye başlandıktan sonra, 1980'lerde taranmaya başlanmıştır. 1991–2005 yılları arasında ülkemizde İstanbul Tıp Fakültesi önderliğinde, lokal bir yenidoğan çalışması yapılarak ilk verilere ulaşılmıştır. Bu araştırmanın sonucunda Dünyada 60.000'de bir sıklıkta olduğu bilinen biyotinidaz eksikliğinin, 11,000'de bir sıklıkta görüldüğü gösterilmiştir. Ülkemizde biyotinidaz yenidoğan taraması 2012 yılında ulusal tarama programına eklenmiş ve sıklığın 5500'de bir olduğu bildirilmiştir. Ulusal tarama verileri İstanbul Üniversitesi'ni destekler bulgular vermiş, en sık görülen bölgenin Kuzeydoğu Anadolu ve en çok hastanın bulunduğu illerin Ardahan, Kars, Iğdır olduğu görülmüştür. Bölgenin tanı konan hastalarının metabolik takibini yapacak merkez sayısı yetersizdir. Sorunun yerinde çözümü için hastaların en sık olduğu illerin başında gelen Kars'ta bulunan Kafkas Üniversitesi'ne bağlı bir "Biyotinidaz Eksikliği Araştırma Enstitüsü" kurulması ihtiyacına dikkat çekebilmek için bu makalenin yazılmasına karar verilmiştir.

Anahtar kelimeler: *biyotinidaz eksikliği; yenidoğan tarama; kalıtsal sağırlık; kalıtsal körlük; demiyelinizan hastalıklar; alopesi; ani bebek ölüm sendromu; genetik hastalıklar*

Introduction

The primary function of the enzyme biotinidase is to separate biotin from biocytin. Biotin acts as a cofactor for four carboxylase enzymes involved in amino acid catabolism, fatty acid synthesis and gluconeogenesis[1]. Biotinidase deficiency (BD) is defined as partial deficiency (activity 10–30% of the mean normal value) and profound deficiency (activity less than 10% of the mean normal value) according to the activity level of the enzyme. However, in cases of partial deficiency, similar clinical signs of a profound deficiency may be observed under catabolic conditions such as infection and starvation[2]. Clinical findings are variable among BD patients. Suppose the patient has epilepsy refractory to conventional treatment, acidosis, dermatitis, unexplained hearing or visual loss, spastic paraparesis and growth retardation. In that case, biotinidase deficiency

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should be considered in the specific diagnosis along with these outcomes[3–10]. Biotinidase deficiency as one of the causes of sudden infant death has also been published[11].

Patients are usually recognised with lactic acidosis, hyperammonemia and characteristic organic aciduria. In urine organic acid analysis, lactic acid, 3-OH-isovaleric acid, methylcrotonyl glycine, and methyl citrate excretion are increased. Cerebral oedema, hypodense areas in the white matter, cerebral atrophy and ventricular enlargement are seen with cranial magnetic resonance imaging (MRI). An increase in lactic acid can be seen on magnetic resonance spectroscopy (MRS). Visual and auditory impairment can be demonstrated by electrophysiological evaluation. Visual evoked potential (VEP), electroretinography (ERG) and brainstem auditory stimulus response (BERA) are used for this purpose[7,9,12].

The treatment of BD with biotin was described for the first time in 1971[11,13]. Wolf et al. provided a detailed clinical description of biotinidase deficiency in the 1980s[1,14–16]. Biotinidase deficiency is an autosomal recessive inherited disease. The cytogenetic localisation of the gene responsible for the disease was identified as 3p25.1 and the genomic coordinates (GRCh38,hg38) were identified as Chr3:15.601.745–15.653.714 (ENST00000643237.3)[17–21]. An economical screening method was described by Heard et al. (1984)[14]. Nowadays, BD tests are screened in many countries. The prevalence is known to be 1 in 60,000 worldwide. However, in a local survey of Istanbul province conducted between 1991 and 2005 at Istanbul University, Istanbul Faculty of Medicine, the prevalence of definite biotinidase deficiency was found to be 1/11144[22,23]. Based on the results of this local screening, it was decided to include biotinidase deficiency in the national newborn screening programme. According to the 2012 national screening results, the prevalence of biotinidase deficiency was found to be ~1/5,500[24]. This value means that the frequency is the highest in the world. The province of Istanbul, where the local screening was conducted, has a population mix of people from all provinces of our country. The provinces from which the screened patients migrated are analyzed in detail, with the prominent ones being Ardahan, Kars, Sivas, and Iğdir, respectively (Fig. 1)[22]. As a result of the national screening programme in 2012, the region with the highest prevalence of biotinidase deficiency in Türkiye was found to be the Northeastern Anatolia region.

Discussion

Dermatological findings in biotinidase deficiency include alopecia and eczematous dermatitis, which are independent of enzyme levels and time of diagnosis, and are defined as the first findings to improve with treatment[5]. However, neurological findings do not respond as satisfactorily to treatment as dermatological findings. Pindolia et al (2010), in a 2010 update on BD mutations and clinical considerations, emphasised that there is a close relationship between the level of enzyme activity and the mutation, and that those with profound deficiency share the same genotype[20]. Also, Swango et al. (1998) also described that the c. 1330G >C mutation causes a 50% loss of enzyme activity[18] and behaves like the Duarte variant described in galactosemia. This mutation has been detected in a family in our province.

In Ankara, Genç et al. (2007) found a 55% frequency of deafness in 20 patients with late-diagnosed BD, and it was observed that hearing was affected in all patients whose diagnosis and treatment were initiated,

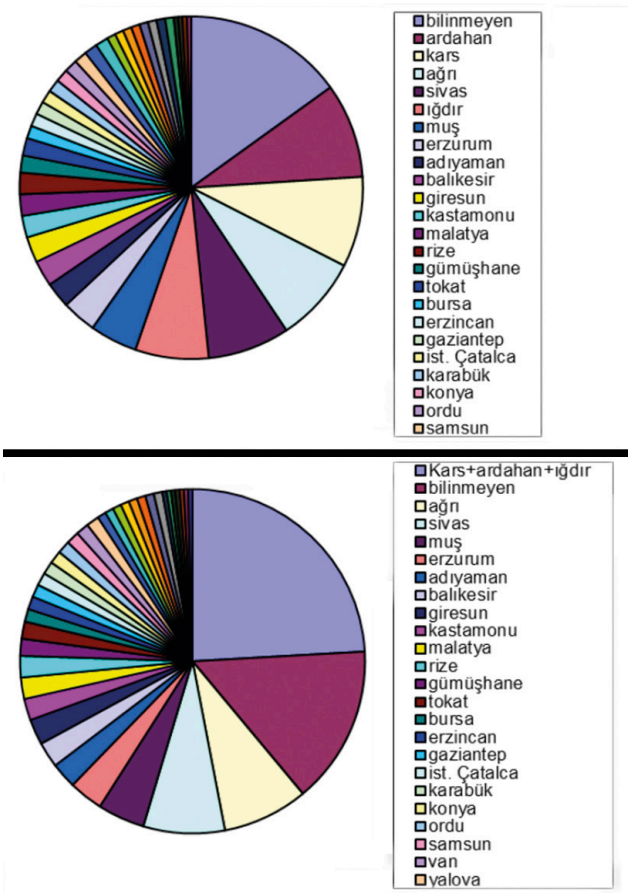

Figure 1. *Distribution of patients diagnosed with biotinidase deficiency according to familial geographical origin.*

particularly after 30 months. Molecular characteristics of these patients were not reported[9]. Sivri– Kalkanoğlu et al. (2007) defined the frequency of deafness as 76% in a group of 20 patients with late diagnosis[10]. Molecular genetic characteristics of these patients: c.98-104Del7ins3 (frameshift) in 4 patients, c.171T >G; p.(57Y >stop) in 4 patients, c.1612C >T; p.(538R >C) in 1 patient, c.194ins4 (frame, shift) in 1 patient, c.1493insT (frame-shift) in 1 patient was identified[10].

Over one year, 23 patients were admitted to the Paediatric Metabolism Clinic of Kafkas University after newborn screening, and 9 of them were diagnosed and followed up. While being followed up by family screening and other centres, 43 patients were included in a clinical follow-up for 1 year, including 20 patients who came to our hospital after the announcement of our department's opening. However, since we are still inadequate in terms of laboratory support in the follow-up of patients, we have to ask for assistance from external laboratories or for help from the facilities of other centres. Among the 10 families in which mutation analysis could be performed, the c.1330G >C mutation was found in 1 patient, the c.1270G >C mutation in 5 patients, and the p. (D242 H) mutation in 4 patients. Six of the patients had significant biotinidase deficiency. All patients who had started follow-up at other centres and continued to our department had been without follow-up and treatment history since the pandemic period.

All patients' families reported that they went to at least two different centres for clinical follow-up and that they were unable to supplement the old clinical follow-up information from the metabolic outpatient clinics, which were closed due to the departure of doctors at the end of the compulsory service period. Old patients had to be re-examined. The metabolic and genetic data of the patients could not be accessed from the electronic patient tracking system of the Ministry of Health of Türkiye. From the neonatal screening system using the mother's identification number, the patient's initial application data has been accessed for the last four months. It has been observed that VEP and BERA scores deteriorate during the period of the patient's loss to clinical follow-up. It was found that none of the families were screened. It was planned to screen and clinically evaluate family members born before the national screening programme began in 2012. However, as there is no genetic laboratory support in our hospital, we try to contribute to the follow-up of patients and their families by preparing projects.

When the geographical distribution and socio-cultural structure of the patients are evaluated, the fact that the screening has Azerbaijani origins in terms of population genetics and that patient information has been available for more than a century, especially in the provinces of Kars, Ardahan, and Iğdir, shows that a collaboration with Azerbaijan, Nakhchivan and Iran is needed. In 2013, the Azerbaijan government initiated screening for phenylketonuria, galactosemia, glucose-6-PO4 dehydrogenase, sickle cell anaemia, thalassaemia, and congenital hypothyroidism; however, it was noted that biotinidase deficiency was not included in the screening programme[25]. It is evident that collaborations should be carried out with neighbouring countries in this regard, and it is also essential for patients to reveal genetic diagnoses.

Conclusion

The number of Paediatric Metabolism doctors responsible for clinical follow-up and treatment in the provinces where the disease is most common is one after 2024, and the number of laboratories to perform confirmatory treatment is zero. If a disease is selected for screening, the screening is a means, a tool, not a goal in itself. The aim is to ensure that a health organisation capable of properly monitoring and treating the screened diseases is employed where necessary and that patients are treated without harm. The realistic, solution-oriented aim is to screen patient or carrier parents, therefore reducing the birth of new patients. Even if it is the prevention of the birth of new patients through preimplantation genetics, it raises ethical concerns. It would be a logical approach to establish a research centre that can achieve this 'Biotinidase Institute' , within Kafkas University, the largest university in the provinces where the disease is most common. Pediatric Metabolism,

Medical Genetics, Pediatric Neurology, Otorhinolaryngology, Ophthalmology, Biochemistry, Obstetrics and Gynaecology doctors should be on the Institute staff. This review has been written to make the situation more visible in its local dimension and to raise awareness of expectations.

Declaration of Interest

The authors declare no conflict of interest.

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