Biotidinase Deficiency Accompanied by Diffuse Demyelination and Cerebral Atrophy

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ABSTRACT

Biotinidase deficiency is an inherited disorder which has autosomal recessive pattern; it occurs in approximately 1 in 60,000 live births. Usually it manifests seborrheic dermatitis, alopecia, ataxia, convulsions, hypotonia, developmental delay, hearing loss, chronic lactic acidosis and immune deficiency. Its diagnosis is made by the measurement of serum biotinidase enzyme activity and determination of the enzyme. Herein presented that a two and half-month-old boy with biotinidase enzyme deficiency which had cerebral atrophy without any skin signs. In the patients presented with refractory convulsions with unexplainable etiology without any skin lesions, as in our patient, biotinidase enzyme deficiency should be considered and the treatment should be established in early period to prevent many complications that may develop.

Key words: *Biotidinase deficiency, demyelination, cerebral atrophy, child*

Yaygın Demiyelizasyon ve Serebral Atrofi ile Seyreden Biotinidaz Eksikliği

ÖZET

Biotinidaz eksikliği yaklaşık olarak 60.000 canlı doğumda bir görülen otozomal resesif geçişli herediter bir hastalıktır. Bu hastalıkta genellikle seboreik dermatit, alopesi, ataksi, konvülsiyon, hipotoni, gelişme geriliği, işitme kaybı, kronik laktik asidoz ve immün yetmezlik görülür. Serumda enzim düzeyi ve aktivitesi ölçülerek tanı konulur. Burada herhangi bir cilt bulgusu olmaksızın serebral atrofi ile başvuran 2,5 aylık erkek biotinidaz olgusu sunulmuştur. Hastamızda olduğu gibi etiyolojisi belli olmayan dirençli konvülsiyonlar ile başvuran ve herhangi bir cilt bulgusu olmayan hastalarda biotinidaz eksikliği göz önünde bulundurulmalıdır. Ayrıca gelişebilecek komplikasyonların önlenmesi için erken dönemde tedavi uygulanmalıdır.

Anahtar kelimeler: *Biotinidaz eksikliği, demiyelizasyon, serebral atrofi, çocuk*

INTRODUCTION

Biotinidase deficiency is an inherited disorder characterized by the inability to separate and reuse of protein-bound biotin. It is inherited in an autosomal recessive pattern. It occurs in approximately one in 60,000 births (1). Biotin is a water-soluble vitamin; it works as a coenzyme for carboxylase enzymes, such as pyruvate carboxylase, propionyl-CoA carboxylase, 3-methylcrotonyle-CoA carboxylase and acetyl-CoA carboxylase. These enzymes are necessary for biosynthesis of fatty acids, gluconeogenesis and catabolism of amino acids (2). Biotinidase deficiency, which may lead to many different clinical features, is usually encountered with the signs of seborrheic dermatitis, alopecia, ataxia, convulsions, hypo-

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tonia, developmental delay, hearing loss, chronic lactic acidosis and immune deficiency. According to the plasma biotinidase enzyme activity levels, the patients are classified as profound deficiency (residual activity is below 10%) or partial deficiency (residual activity is in a range of 10-30%). If the disease remains untreated, the symptoms worsen, coma and death may occur (2). In this study, a two and half-month-old boy patient presented with diffuse demyelination and cerebral atrophy who had biotinidase enzyme deficiency was presented.

CASE

A two and half-month-old boy patient was presented with the complaints of abdominal distention, drowsiness and poor feeding. It was learned that abdominal distention had emerged 15 days after delivery and he had continuous drowsiness for the last 5 days. It was indicated that the patient, who did not have any pathologic properties in his own and family medical stories, had not recognized his mother yet and was not able to hold his head up. In the newborn period, he was hospitalized for 10 days and given treatment because of urinary tract infection. The patient was given treatment with the diagnosis of gastroenteritis in the hospital to which he was admitted with the complaint of poor feeding, but in follow up the patient did not show any improvement and presented to our hospital. On physical examination, he had moderate dehydration, acidotic breathing, hepatomegaly, diffuse dermatitis on perineal area; neurologic examination revealed lack of following object and light, prominent hypotonia, normoactive deep tendon reflexes and preconvulsive movements. His body weight was 5 kg (10-25 percentile), his height was 54 cm (3-10 percentile) and his head circumference was 40 cm (25-50 percentile), his vital signs were within normal limits. Among laboratory tests, hematologic parameters, serum electrolytes, liver and renal function tests and blood ammoniac level were normal. Serum lactic acid level was high in the patient who had severe metabolic acidosis. In the cerebrospinal fluid analysis, protein, glucose and chlorine levels were found to be 98 mg/dL, 61 mg/dL, and 127 mEq/L, respectively. Simultaneous blood glucose level was found to be 65 mg/dL. Cultures of blood, urine and cerebrospinal fluid did not yield any microbiologic growth. The patient was given proper fluid replacement for dehydration and sodium bicarbonate treatment for acidosis. The patient who had convulsion was initialised phenobarbital. Cranial magnetic resonance imaging and computed tomography revealed cerebral atrophy and diffuse demyelinated areas more prominent in bilateral fronto-temporal regions (Figure 1 A and B). Biotinidase enzyme activity was found to be 0 enzyme unit (N>62.5 enzyme unit) according to the Tandem Mass metabolic disease screening panel. The patient was started biotin in a dose of 10 mg per day. On the second day of biotin treatment, metabolic acidosis was improved. One week after biotin intake, it was observed that convulsions were disappeared, his general status was significantly improved and poor feeding was disappeared. The patient progresses with normal development process without any attacks and is still under outpatient follow up.

DISCUSSION

Biotin taken by diet is bound to protein (biocytin or biotinylated peptides). Biotin is released within intestines by the effects of digestive enzymes and biotinidase enzyme. Biotinidase enzyme that exists in many tissues and serum in human body is an enzyme necessary for the release of biotin from protein and the use of biotin in the body. Free biotin activates carboxylase enzymes binding with covalent binds to apoproteins located on these enzymes (3). Disorders of biotin use are reviewed under the heading of "multiple carboxylase deficiencies". Multiple carboxylase deficiencies are divided into two groups, holocarboxylase synthetase deficiency (infantile or early form) and biotinidase deficiency (juvenile or late form). In general, holocarboxylase synthetase deficiency and biotinidase deficiency lead to similar manifestations (4,5). The symptoms occur within the first few weeks of life in holocarboxylase synthetase deficiency, whereas in biotinidase deficiency, symptoms may emerge months or years later (6).

The patients with biotinidase deficiency are usually presented because of hypotonia, convulsions, lactic acidosis, respiratory problems (e.g. tachypnea, apnea), vomiting and developmental delay (4,6). The most important clinical feature distinguishing biotinidase deficiency from other organic acidemias is that skin signs are far more prominent (6). In these patients, atopic or seborrheic dermatitis, alopecia, exfoliative erythematous lesions may be seen. In some cases, hearing loss, immune deficiency, optic atrophy, conjunctivitis and ataxia may also be found (2,6,7). That our patient did not have skin lesions accepted as a characteristic feature of biotinidase enzyme deficiency, although he had convulsions, hypoto-

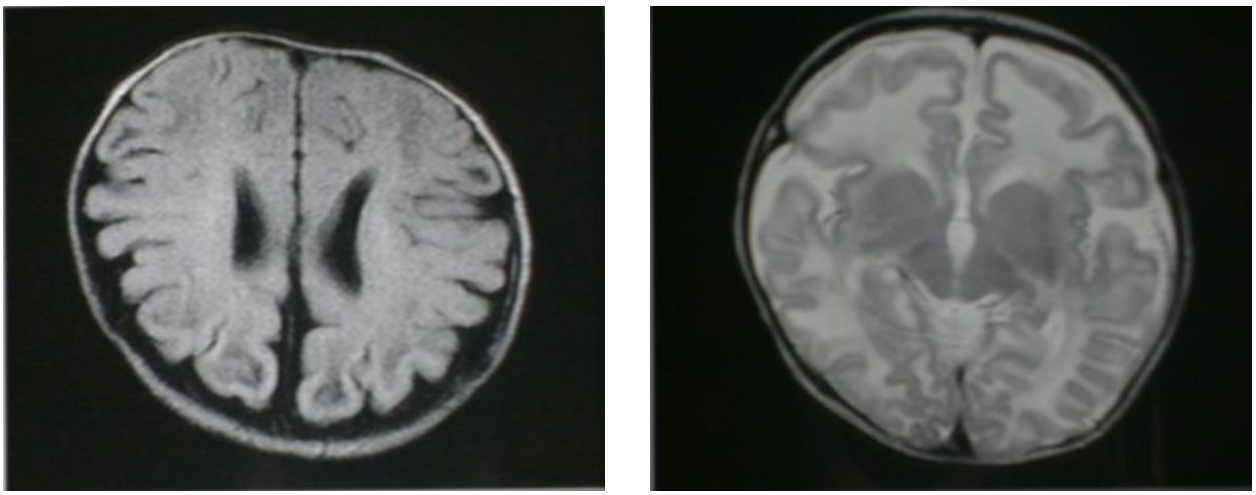

***Figure 1 A and B**. Cranial magnetic resonance imaging and computed tomography revealed cerebral atrophy and diffuse demyelinated areas more prominent in bilateral fronto-temporal regions.*

nia, lactic acidosis, vomiting and tachypnea, as does typical patients with biotinidase enzyme deficiency, suggests that skin lesions are not essential properties in biotinidase enzyme deficiency. Hence, further investigation of the patients having characteristic of biotinidase enzyme deficiency but not skin lesions for biotinidase enzyme deficiency may be beneficial.

In the laboratory tests of the patients with biotinidase enzyme deficiency, metabolic acidosis, ketosis, rises in organic acids (lactic acid, propionic acid, 3-methyl crotonic acid) in body fluids and high levels of serum ammoniac are found (4,6,8). The diagnosis is made by the measurement of serum biotinidase enzyme activity and determination of the enzyme (6). Affected patients respond dramatically to biotin (10-20 mg daily). Biotinidase enzyme deficiency is a disorder that its treatment is more economical and easier than other metabolic diseases (5). In a patient manifesting metabolic acidosis episodes and neurologic signs, it should be considered if there are also accompanying skin lesions; the diagnosis should be confirmed by measurements of serum biotinidase activity and enzyme itself (8). In emergent situations, the treatment should be established promptly after collection of serum and urine samples that are necessary for the diagnosis. Metabolic acidosis, skin lesions, keratoconjunctivitis, lactic and pyruvic academia, organic aciduria are improved in a short period as a consequence of the treatment, however, it has been reported that visual and hearing losses are irreversible (3,9). Prompt diagnosis and treatment of this disease is important to prevent sequels emerging in central nervous system and life saving.

In the patients appealing with refractory convulsions with unexplainable etiology without skin lesions, as in our patient, one should be aware of biotinidase enzyme deficiency and treatment should be established immediately to prevent many complications that may develop.

REFERENCES

1. *Wolf B, Grier RE, Secor McVoy JR, Heard GS. Biotinidase deficiency: a novel vitamin recycling defect. J Inherit Metab Dis 1985;8:53-8*
2. *Hoffman TL, Simon EM, Ficicioglu C. Biotinidasedeficiency: the importance of adequate follow-up for aninconclusive newborn screening result. Eur J Pediatr 2005;164:298-301*
3. *Baykal T, Huner G, Sarbat G, Demirkol M. Incidence of biotinidase deficiency in Turkish new-borns. Acta Pediatr 1998;87:1102-3*
4. *Hou JW. Biotin responsive multiple carboxylase deficiency presenting as diabetic ketoacidosis. Chang Gung Med J 2004;27:129-33*
5. *Wolf B. Biotinidase Deficiency: New Directions and Practical Concerns. Curr Treat Options Neurol 2003;5:321-8*
6. *Neto EC, Schulte J, Rubim R, et al. Newborn screening for biotinidase deficiency in Brazil: biochemical and molecular characterizations. Braz J Med Biol Res 2004;37:295-9*
7. *Puertas Bordallo D, Martín Reyes C, Ruiz-Falcó Rojas ML, Duat Rodríguez A, Valls Ferrán MI. Optic neuropathy in bi-*

otinidase deficiency. Arch Soc Esp Oftalmol 2004;79:393-6

8. Yang YL, Yamaguchi S, Tagami Y, et al. Diagnosis and treatment of biotinidase deficiency-clinical study of six patients. Zhonghua Er Ke Za Zhi 2003;41:249-51

9. Möslinger D, Mühl A, Suormala T, Baumgartner R, Stöckler-Ipsiroglu S. Molecular characterisation and neuropsychological outcome of 21 patients with profound biotinidase deficiency detected by newborn screening and family studies. Eur J Pediatr 2003;162:46-9