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A Patient Diagnosed with Li-Campeau Syndrome and Biotinidase Deficiency

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Abstract

Biotinidase (BTD) enzyme deficiency is a congenital metabolic disorder with autosomal recessive inheritance. Main symptoms in its deficiency are nervous system and skin manifestations. A 15-month-old patient who was diagnosed with Li-Campeau syndrome, was also diagnosed with BTD deficiency and his clinic rapidly improved with biotin treatment. With the awareness of different clinical presentations of BTD deficiency, patients presenting with clinical symptoms raising the suspicion of this disorder must be evaluated for enzyme activity and genetic analysis must be planned. It is of great importance to keep in mind the possibility of this rare but treatable neurometabolic disorder, even in countries with neonatal screening programme and include it in differential diagnoses in order to prevent irreversible symptoms.

Keywords: Biotinidase deficiency, partial, clinical findings, treatment

Introduction

Biotinidase (BTD) deficiency is an autosomal recessive metabolic disorder presenting with neurocutaneous manifestations for which mutations in *BTD* gene are responsible. BTD is an enzyme required for the formation of biotin through a cascade of reactions called biotin turnover and it is involved in biotin recycling in the body. In BTD deficiency, the body is unable to recycle vitamin biotin, resulting in a decrease in biotin levels in the body. The disorder can present with a variety of clinical manifestations including alopecia, dermatitis, ataxia, convulsions, hypotonia, growth retardation, and hearing loss. Patients are grouped as having either profound (residual activity <10% of mean activity) or partial (residual activity <10-30% of mean activity) deficiency depending on the plasma enzyme activity.[1-3] The incidence rate is 1 in 60.000 people. Turkey is one of the countries with the highest incidence rates.[3-5] Thus, the newborns are screened as part of the National Neonatal Screening Program since October 2008.[4] The screening program aims to diagnose the condition in the early period and instigate early therapy before the development of irreversible symptoms such as permanent hearing loss, optic atrophy and global growth retardation in the long term.[6] Our patient who had dysmorphic facial features, neurodevelopmental delay, hypotonia, seizures, cardiac system abnormalities was diagnosed with

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Li-Campeau syndrome (LICAS), a neurodevelopmental disorder characterized by global developmental delay, impaired intellectual development, variable abnormalities of cardiac and genital system, hypotonia, seizures and dysmorphic features.[7] The patient, who had skin findings in addition to neurological findings, was also evaluated in terms of BTD deficiency. The current report presents a case of LICAS who was diagnosed with BTD deficiency. The patient's guardian provided informed consent for publishing this study.

Case Report

A 15-month-old male patient presented to pediatric neurology outpatient clinic due to hypotonia, growth retardation, feeding problems, vomiting and diarrhea. The patient had been diagnosed with growth retardation during intrauterine period and been delivered by Cesarean section at 38 weeks of gestation and with a birth weight of 2010 gr. He had been intubated due to respiratory distress immediately after birth. The patient was born as the third child to a 31-year-old healthy mother and her first cousin, 32-year-old healthy father. He had two siblings one of whom was healthy and the other was on follow-up with the diagnosis of autism. The patient did not have a family history of chronic disease. In his medical history, he had suffered from respiratory and feeding problems since birth, had sucking and swallowing dysfunctions as well as growth retardation and developmental delay. A percutaneous endoscopic gastrostomy (PEG) tube had been inserted at seven months due to sustained feeding problems. The patient had frequent hospitalizations due to respiratory and gastrointestinal tract infections. Antiepileptic drug had been initiated at six months due to focal onset motor seizures with impaired awareness that were controlled by the given therapy. Electoencephalography (EEG) was normal. The patient had a recurrent seizure one year after, during a period of infection for which the dose of antiepileptic drug had been increased. The patient did not have any seizures thereafter and was on a therapy with levetiracetam at 30 mg/kg/day.

The vital signs were stable on physical examination. The body weight was 6.4 kg (<3rd percentile), the height was 78 cm (<3rd percentile) and the head circumference was 43 cm (<3rd percentile). The patient was aware of his surroundings, had social smile and was able to use a few words. On physical examination, the patient was found to have epicantal fold, downslanting palpebral fissures, ptosis, hypertelorism, low set ears, prominent forehead, thick but weak eyebrows, hypertrichosis and long fingers (**Figure 1a, b**). The skin was dry and the hair was weak. The patient had head control, was able to sit with support for a short period and had trunk hypotonia (**Figure 1a, b**). Muscle tone was increased bilaterally in the lower extremities and he had brisk deep tendon reflexes. He had bilateral cortical thumbs. Hearing and visual examination revealed normal findings. Cardiac examination revealed secundum atrial septal defect and patent ductus arteriosus. The patient did not have oral intake due to lack of sucking-chewing-swallowing functions and was fed with a PEG tube.

From laboratory tests, hematological parameters, serum electrolytes, thyroid function tests, vitamin B12, liver and kidney function tests, arterial blood gas analysis, serum ammonia, plasma and urine amino acid results were within normal ranges. Urine organic acids were normal. Cranial magnetic resonance imaging revealed no abnormal findings. An examination of the *UBR7* gene revealed a homozygous frameshift mutation (ENST00000013070.6)(c.1192_1193 del) and as a result, the patient was diagnosed with LICAS. Even after a neonatal screening turned out to be negative, BTD activity was also studied during metabolic testing, since the patient had skin and some neurological findings that were inconsistent with the diagnosis. Suprisingly, the enzyme activity was found to be 23% (normal if >30%), suggesting partial (10-30%) BTD deficiency. The patient was placed on biotin therapy at a daily dose of 5 mg/day based on clinical findings, and further genetic analysis was foreplanned. The patient showed rapid improvements in his clinical condition during the follow-up visit at two weeks. The patient was able to sit without support, turn and stand up with support for a short period; spasticity decreased; the patient was able to take liquid oral food and showed increased awareness of his surroundings. Vomiting and diarrhea have also improved. Improvements in drinking and swallowing functions were also noted at one-month control examination. The patient was able to stand up for a longer period and showed an

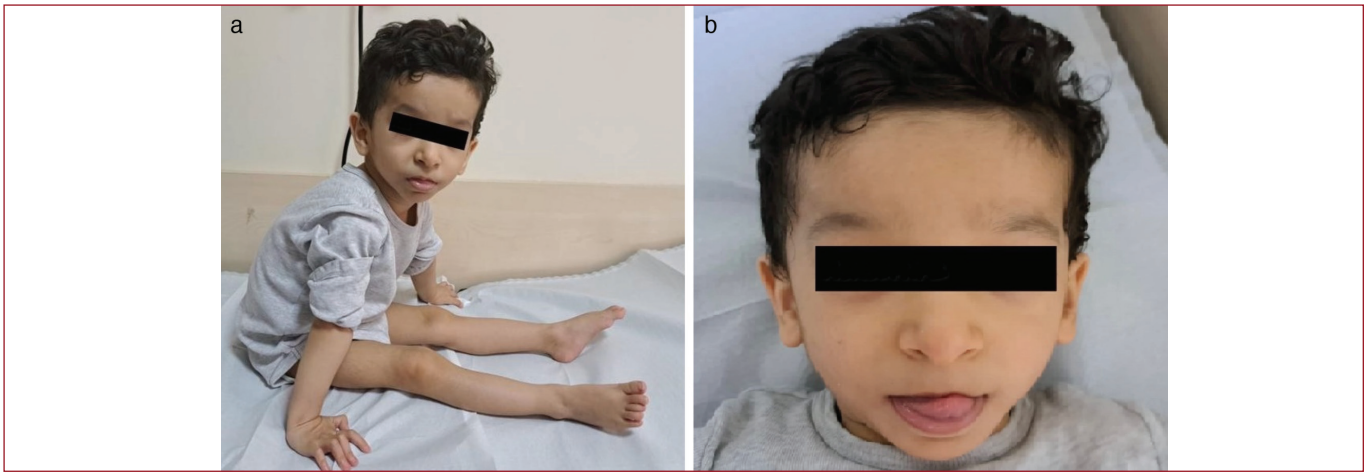

Figure 1. Characteristic features of the patient; **a)** Clinical features (hypotonia, long fingers, prominent forehead, hypertrichosis), **b)** Dysmorphic facial features (epicantal fold, ptosis, low set ears, hypertelorism).

increased awareness of his surroundings along with an improvement in his speech. Genetic analyses performed to support the diagnosis revealed heterozygous missense variation (ENST00000437172.1) c.1336G>C (p.D446H) and heterozygous missense variation (ENST00000437172.1) c.974A>G (p.H325R) in the *BTD* gene, classified as pathogenic and likely pathogenic, respectively. In molecular genetic analysis of the mother and the father, it was found that the c.1336G>C variant was originated from the father and the c.974A>G variant was originated from the mother, and these two variants were compound heterozygous in the probant.

Because patients with BTD deficiency present with a variety of clinical symptoms and rarely with the symptoms of autism, BTD enzyme activity was also evaluated in the 9-year-old older sister who had symptoms of autism. BTD enzyme activity of the sister was found to be 32% (normal if >30%). The sister was placed on biotin therapy at a daily dose of 5 mg/day due to levels close to the lower limits of normal. Laboratory tests and cranial imaging study revealed no pathological findings. Genetic analysis did not reveal any mutations in *BTD* gene, and thus ruled out BTD deficiency.

The patient was put on biotin therapy at a daly dose of 5 mg/day and a month later the dose was increased to 10 mg/day due to lack of complete clinical response. Despite the improvements with biotin therapy initially, there were no further clinical improvements with the increase in the daily dose and his neuromotor development was still not up to the normal range. The patient continues to attend outpatient visits and is back on 5 mg/day biotin therapy as well as rehabilitation and mental health support programmes.

Our patient, who was followed up with the diagnosis of LICAS syndrome, was also diagnosed with BTD deficiency. To the best of our knowledge, the presence of the two diseases in the same patient was not reported in the literature.

Discussion

BTD deficiency is common and the incidence rates in Turkey are known to be higher than the world's average due to frequent consanguineous marriages.[4] The gene responsible for BTD synthesis is located in the 3p25 region with more than 240 genetic alterations associated with the disorder.[3] The mutations that cause enzyme deficiency include "missense", "nonsense", single or multiple nucleotide deletion or insertion, and "cryptic splice site" mutations. Genotype-phenotype relationship is not clear in BTD deficiency. Deletion/insertion and "nonsense" mutations result in the absence of enzyme activity, while "missense" mutations may not cause complete absence of the enzyme activity. In cases of deficiency, carboxylases requiring biotin for their activity stop functioning.[2] Development of symptoms is inevitable in patients with profound enzyme deficiency, while patients with partial deficiency present with milder symptoms. Clinical symptoms occur generally in the first 3-6 months. The patients may present with a wide variety of clinical symptoms and complaints with an acute or chronic clinical course. In cases of attacks, patients often present with feeding and respiratory problems, alopecia, skin rash, seizures, hypotonia and ataxia. Feeding problems, vomiting and retching are observed in bulbar involvement and respiratory problems include apnea, stridor and hyperventilation. Developmental delay, conjunctivitis, fungal infections, recurrent upper respiratory tract infections and lung infections, optic atrophy and visual problems, and hearing loss are other clinical presentations.[2-4] Laboratory tests can show metabolic acidosis, ketosis, increase in organic acids and hyperammoniemia. Diagnosis is based on measurement of serum BTD activity and molecular genetic studies. The enzyme activity must be evaluated with repeated measurements for precise classification of the disorder and deliver appropriate therapy because BTD enzyme activity shows physiological variations during the day.[1,2,4] The patient's sister who was diagnosed with autism at the age of two had an enzyme activity of 32%, but the results of molecular genetic analysis did not support those findings and as a result of that, BTD deficiency was ruled out.

The affected patients respond dramatically to biotin therapy. Even though early biotin therapy can prevent development of symptoms, neurological damage in symptomatic patients may not always be reversible. Therefore, it is of great importance to establish early diagnosis and start early therapy to prevent the sequels in the central nervous system. As in the reported patient, the clinicians must be vigilant about the possibility of BTD deficiency in patients presenting with skin findings, hypotonia, vomiting and respiratory symptoms even if neonatal screening tests turn out to be negative, and early therapy must be initiated before the development of permanent complications.[2,4] Clinical symptoms develop over time in untreated patients and BTD enzyme deficiency may not be considered by the clinician in the countries implementing neonatal screening programs, as the symptoms are not specific and can be associated with other etiologies. So we evaluated patient it in terms of BTD deficiency. Although dysmorphic features such as prominent forehead, hypertelorism, low-set ears, epicanthal folds, ptosis, long fingers, hypertichosis; gastrointestinal dysmotility, developmental delay, hypotonia, seizure and congenital cardiac defects were typically associated with LICAS, skin and hair findings were inconsistent with the diagnosis. The coexistence of neurological and cutaneous findings led us to the differential diagnosis of BTD deficiency.

Neonatal screening programs using a fluorometric method have reported a sensitivity of 100% and a specificity of 97%, while a sensitivity of 90.5% and a specificity of 93.7% has been reported for spectrophotometric method. The percentage of patients found to have normal enzyme activity using spectrophotometric method, but still have this condition was reported as 9.5%, which is a significant rate.[8] The diagnosis is challenging in patients presenting with atypical and mild clinical symptoms. It is crucial to consider the diagnosis in those presenting with atypical symptoms. The symptoms in BTD deficiency are not solely dependent on the enzyme activity, but also affected by other factors such as exogenous biotin intake and biotin requirement in metabolic pathways.

The symptoms in patients with partial BTD deficiency can be milder than those with profound deficiency; however, symptoms may still be present such as skin rash, alopecia, ataxia, hypotonia and developmental delay. Most symptoms disappear with biotin therapy. Clinical symptoms such as hypotonia, seizures and skin rash can occur in partial enzyme deficiency, but keto-or lactic acidosis and organic aciduria may not be observed due to preserved carboxylase enzyme activity. Organic acidemia is observed in relation to the dysfunction of carboxylation enzymes in patients with profound BTD deficiency.[2,4,6,9] Seizure is a frequent symptom in patients with BTD deficiency, even it may be a presentng symptom. Impairment in the function of biotin-dependent carboxylases causes accumulation of neurotoxic and epileptogenic metabolites.[4] Seizures are usually generalized tonic-clonic, but there have also been described some patients with myoclonic seizures, focal seizures and infantile spasms. EEGs can be normal or mostly abnormal with burst attenuation pattern or epileptiform discharges. Cranial imaging studies show no pathological findings in the majority of patients with symptomatic BTD deficiency, but cerebral/cerebellar atrophy, cerebral edema, calcification in basal ganglia, ventriculomegaly and a decrease in the volume of white matter are the most common findings in those with pathological findings based on imaging studies.[4,10]

Biotin therapy is delivered at a dose of 5 mg/day in patients with partial enzyme deficiency and the dose may be increased to 10 mg/day in the absence of complete clinical response. The compliance of the patient to therapy is as important as the diagnosis. Patients placed on therapy during the presymtomatic period and receiving life-long therapy are known to have good prognosis. The symptoms may disappear, or become less severe or at least remain stable in patients who are put on a therapy in the symptomatic period.[2,4,6,11]

Conclusion

More than one disease can be seen in a patient. Therefore, patients may present with the symptoms of both diseases. BTD deficiency is quite common in our society and therefore, children with dermatological and neurological manifestations among its wide variety of symptoms must be evaluated for it. Analysis of the enzyme activity and genetic tests are recommended, even in patients with a negative test result as a part of the neonatal screening program, if the clinical symptoms suggest enzyme deficiency. Clinical symptoms recover rapidly with early therapy and the outcomes are satisfactory in those receiving regular life-long therapy.

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