



CITRULLINEMIA ASSOCIATED WITH CONGENITAL HYPOTHYROIDISM

KONJENİTAL HİPOTİROİDİNİN EŞLİK ETTİĞİ SİTRÜLLİNEMİ

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Anahtar sözcükler: sitrüllinemi, konjenital hipotiroidi, yenidoğan

Key words: citrullinemia, congenital hypothyroidism, neonate

SUMMARY

Neonatal-onset of argininosuccinic acid synthetase deficiency (ASD; citrullinemia) is the most severe form of urea cycle disorders and presents a fatal course with vomiting, feeding difficulty, irritability, lethargy, hypotonia, apnea, convulsion, stupor and coma. The prognosis and quality of life of patients with citrullinemia might be improved with early diagnosis and appropriate therapy. Congenital hypothyroidism is the causal effect of hypotonia in newborns, too.

We report a male infant with neonatal citrullinemia and congenital hypothyroidism who was treated with specific therapeutic protocols designed to activate alternative pathways of waste nitrogen excretion. Congenital hypothyroidism should be brought in mind in the differential diagnosis of hypotonia in neonates with inborn errors of metabolic diseases.

ÖZET

Yenidoğan döneminde başlayan arjininosüksinik asid sentetaz enzim eksikliği üre siklüs hastalıklarının en ağır formudur. Kusma, beslenme güçlüğü, huzursuzluk, uykuya eğilim, hipotoni, apne, konvülsiyon, stupor ve komaya kadar ilerleyebilen ve ölümlü sonuçlanabilen bir hastalıktır. Sitrüllinemili hastaların prognozu ve yaşam kalitesi erken tanı ve uygun tedavi ile düzeltilebilir. Konjenital hipotiroidi de yenidoğanlardaki hipotoni nedenlerinden biridir.

Biz bu yazıda konjenital hipotiroidiyle birlikte neonatal sitrüllinemisi olan ve üre siklüs hastalıklarında uygulanan spesifik tedavi protokolüne göre tedavi edilen bir erkek olguyu sunduk. Doğumsal metabolizma hastalıklarında görülen hipotoninin ayırıcı tanısında konjenital hipotiroidi de akılda bulundurulmalıdır. Neonatal sitrüllinemi ile konjenital hipotiroidi birlikteliğine ulaşılabilen kaynaklarda rastlanamadığından dolayı olgu ilginç bulunarak sunulmuştur.

INTRODUCTION

Citrullinemia is an inborn error of urea cycle metabolism, with autosomal recessive inheritance, caused by deficient argininosuccinate synthetase. There is considerable phenotypic variability; the most common and severe clinical presentation is the neonatal form characterized by rapidly progressive encephalopathy and death^{1,2}. Severe hyperammonemia often leads to

brain edema, coma, or permanent neurologic sequelae³. Early diagnosis and aggressive therapy of hyperammonemia improve the long-term developmental outcome of affected survivors. Hypotonia and lethargy are also clinical manifestations of congenital hypothyroidism, but muscular hypotonia is rarely generalizing in congenital hypothyroidism⁴. We present here, a newborn with citrullinemia associated with congenital hypothyroidism.

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Makalenin teslim tarihi: 30.03.2004; kabul tarihi: 03.05.2004

CASE REPORT

A male infant was born to a healthy 38 year-old mother at 40 weeks gestation after an uneventful pregnancy. He was the fourth child of consanguineous parents. Apgar score was 9 at 1 minute and 5 minutes. The birth weight was 2980 g, length was 50 cm, and head circumference was 36 cm. The two previous siblings had been normal at birth, but had become lethargic on the fourth day of life and died. The infant was normal at birth. During the first two days of life, the infant seemed normal and was feeding well. He became hypotonic and had difficulty in feeding on the third day. He became increasingly lethargic on the fifth day. On the sixth day, he was admitted to hospital, exhibiting intermittent depressed breathing. The lethargy progressed to coma and he had respiratory arrest requiring intubation and mechanical ventilation. Physical examination revealed a deeply encephalopathy. The Moro and other reflexes were absent. There was a family history suggestive of inborn errors of metabolism. Diagnosis was based on elevated plasma ammonium level (814 $\mu\text{mol/L}$), increased plasma and urine citrulline levels (699 $\mu\text{mol/L}$ and 17313 $\mu\text{mol/L}$) and normal plasma argininosuccinate level (0.01 $\mu\text{mol/L}$). Simultaneously, routine screening of thyroid function test revealed congenital hypothyroidism (On the 10th and the 18th days of life, total T4: 3,9 $\mu\text{g/dl}$, TSH: 20.8 mIU/ml and 4.1 $\mu\text{g/dl}$, 53.7 mIU/ml, respectively) and the replacement therapy was begun. After the diagnosis of ASD, the classic treatment was initiated. Treatment included protein restriction, oral sodium benzoate and arginine supplementation, and exchange transfusions. His plasma ammonium level returned to normal. He was discharged at the age of one month with oral therapy in accordance with specific therapeutic protocols. He died due to hyperammonemic crisis caused by severe infection at the age of 13 months.

DISCUSSION

Neonatal hyperammonemia is a medical emergency requiring early therapy. Urea cycle disorders are the primary cause of hyperammonemia during neonatal period and hyperammonemia occurs with varying severity in these disorders. The urea cycle disorders are caused by defect in the enzymes carbamoyl phosphate synthetase (CPS), ornithine transcarbamylase (OTC), synthetase (citrullinemia), argininosuccinic acid lyase (argininosuccinic aciduria), arginase (hyperargininemia), and N-acetylglutamate synthetase⁵⁻⁷. Except for OTC deficiency, which is inherited as a partially dominant X-linked trait, all other known urea cycle disorders are transmitted as autosomal recessive traits. Citrullinemia is one of urea cycle defects and is caused by argininosuccinic acid synthetase deficiency which includes a failure to synthesize urea, resulting in the accumulation of ammonium, glutamine, and citrulline. The neonatal form

presents the most severe onset and a fatal course with vomiting, failure to feeding, irritability, apnea, convulsion, lethargy, stupor and coma with respiratory arrest^{1,3,8}. Although citrullinemia is reported as a rare urea cycle disorder, ASD was the most commonly determined enzymatic defect in Turkey, because of high rate of consanguineous marriages^{8,9}.

Early and aggressive treatment which consists of protein restriction, administration of arginine HCl, sodium benzoate, sodium phenylacetate and, hemodialysis, the acutely ill infant can be rescued, but frequently has permanent neurological sequelae because of the toxic effects of ammonemia. Patients who have been in a hyperammonemic coma for several days have an extremely poor neurologic outcome. Although the patient may be rapidly detoxified and stabilized, the damage to the brain is likely to be permanent. Our patient was treated with classic therapy protocol of ASD, when the diagnosis was made. His neurologic status improved and ammonia levels returned to normal neonatal range after one week of treatment (73 $\mu\text{mol/L}$).

Before alternate therapy protocol was developed, almost all children with neonatal-onset disease died rapidly. However, survival has improved with the recommended protocol for long-term therapy^{3,6}. Although mortality has decreased, morbidity remains high in children with a neonatal-onset urea cycle disorders. Mental retardation, cerebral palsy, and seizure disorders are the permanent neurologic sequelae of these children^{2,3,5}. All surviving patients have had intercurrent life-threatening hyperammonemic episodes. Precipitating catabolic events such as viral or bacterial infections, trauma, ingestion of large amounts of protein, or other metabolic stresses, and interruption of medications can cause hyperammonemic crisis. These episodes can lead to coma, or death. Our case died during a hyperammonemic episode because of severe bacterial infection at 13 months of life.

Congenital hypothyroidism was also detected by routine screening of the thyroid function test during the treatment of ASD on the 10th day of life and the replacement therapy was begun. Muscular hypotonia and lethargy are also seen at congenital hypothyroidism. It is assumed that neonatal form of citrullinemia with congenital hypothyroidism enhanced hypotonia that was present. The differential diagnosis of hypotonia that is present in inborn errors of metabolic diseases, congenital hypothyroidism should be brought in mind. In conclusion, early diagnosis and treatment of patients with neonatal onset of ASD seem most important in predicting a good outcome.

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