OLGU SUNUMU CASE REPORT

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An Altered Mental Status and Hyperammonemia Attack in an Adolescent Girl: Carnitine Palmitoyltransferase Type 1a (CPT1a) Deficiency

Ergenlik Döneminde Bir Kız Çocuğunda Bilinç Değişikliği ve Hiperamonemi Atağı: Karnitin Palmitoiltransferaz Tip 1a (CPT1A) Eksikliği

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ABSTRACT Hyperammonemia is a characteristic feature of the urea cycle defects and organic acidemias but it may also accompany some other metabolic disorders or hepatic dysfunction. Additionally, some drugs and various toxins may cause elevated ammonia levels. A girl patient presented with vomiting and hypoglycemia attack when she was 2.5 years old. Ten years later, when she was 12.5 years old, she was admitted to the emergency department with severe vomiting attack, and then loss of consciousness totally. Laboratory investigations revealed mildly elevated liver enzymes and hyperammonemia. Free carnitine level was detected very highly elevated in tandem mass analysis. Carnitine palmitoyltransferase type 1a (CPT1a) deficiency was suggested in the patient and, molecular genetic analysis showed homozygous c.364_365dupAT pathogenic variant in the CPT1A gene. High-carbohydrate diet that is low in fat was commenced. She has no neurological sequelae. Elevated carnitin levels and hyperamonemia together with hypoketosis sh.ould be alarming for CPT1a deficiency.

Keywords: Hyperammonemia; carnitine palmitoyltransferase type 1a deficiency

ÖZET Hiperamonemi, üre döngüsü bozuklukları ve organik asidemilerin karakteristik bulgusudur. Bunun yanında başka metabolik hastalıklara, karaciğer fonksiyon bozukluğuna eşlik edebilir. Bazı ilaçlar ve toksinler, hiperamonemi nedeni olabilir. İki buçuk yaşında iken kusma ve hipoglisemi nedeni ile hastaneye başvurusu olan kız hasta, 10 yıl sonra 12,5 yaşında iken ağır seyreden bir kusma atağı arkasından bilinç kaybı ile acil servise başvurdu. Laboratuvar incelemelerinde hafif yüksek karaciğer enzim düzeyleri, üre, laktat ve hiperamonemi görüldü. Ardışık kütle spektroskopisinde, çok yüksek serbest karnitin düzeyleri saptandı. Karnitin palmitoiltransferaz 1a [carnitine palmitoyltransferase type 1a (CPT1a)] eksikliği düşünüldü. Moleküler genetik analizde CPT1A geninde homozigot c.364_365dupAT patojenik varyantı saptandı. Düşük yağ, yüksek karbonhidrat içeren diyet başlandı. Nörolojik sekelsiz olarak iyileşme görüldü. Hipoketozis ile birlikte yüksek karnitin düzeyleri ve hiperamonemi, CPT1a eksikliği yönünden uyarıcı olmalıdır.

Anahtar Kelimeler: Hiperamonemi; karnitin palmitoiltransferaz tip 1a eksikliği

Alteration in the level of consciousness is one of the common pediatric emergencies. Many disorders should be considered in a patient with an altered mental status. Various toxins, drugs, metabolic and infectious causes and broad spectum of supratentorial and infratentorial structural lesions should be considered in the differential diagnosis. Appropriate medical management promptly depends on underlying etiology. Hyperammonemia is one of the well recognized causes of altered mental status and encephalopathy. It is a characteristic feature of the urea cycle defects and organic acidemias but it may also accompany some other fatty acid oxidation defects, mitochondrial diseases or hepatic dysfunction. Additionally, some drugs and various toxins may cause elevated ammonia levels. Diagnosis or treatment delay for hyper-

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ammonemia may lead to neurologic damage and potentially fatal outcome regardless of etiology.[1] Concurrently with urgent treatments for decreasing ammonia levels, hyperammonemia etiology should be investigated with more specialized analyses including serum and urinary amino acids, tandem mass spectrometry, urine organic acids and specific treatment for the underlying etiology should be initiated. Here, we report a Turkish girl patient who was diagnosed with carnitine palmitoyltransferase type 1a (CPT1a) deficiency at 12.5 years old after an attack of hyperammonemia and altered state of consciousness.

CASE REPORT

A girl patient presented with vomiting and hypoglycemia attack when she was 2.5 years old. Ketone levels were low. At that time, enzyme analysis for fructose 1,6 biphosphatase revealed borderline low levels and diagnosis of fructose 1,6 biphosphatase deficiency had been considered. The mutation was not found. In the follow up period, she had only hepatosteatosis, mildly elevated liver enzyme levels and rare episodes of vomiting triggered by infections. She had no accompanying hyperammonemia. Growth and development were normal.

Ten years later, when she was 12.5 years old, she was admitted to the emergency department with consciousness disturbance after a severe vomiting attack, and then loss of consciousness totally. Laboratory investigations revealed mild leucocytosis, mildly elevated liver enzymes, urea and lactate, elevated acute phase reactants, and hyperammonemia. They were as follows: White blood cell (WBC): 15,000/µL, Hemoglobin (Hgb): 12 g/dL, Platelet (Plt): 296,000/µL, Glucose: 81 mg/dL, Aspartate amino transferase (AST): 38 U/L (0-35), Alanine aminotransferase (ALT): 112 U/L (0-35), Uric acid 5.8 mg/dL, Urea: 43 mg/dL (11-39), Creatinine: 0.64 mg/dL (0.5-1.2), Na: 139 mmol/L, K: 4.69 mmol/L, Ca: 10.8 mg/dL, C-reactive protein (CRP): 4.55 mg/dL (0-0.5), pH: 7.36, HCO3-: 22.7 mmol/L 21.8-26.2, Lactate: 3.9 mmol/L (0.5-1.6), Ammonia: 434 µmol/L (17-57). She had no ketosis. Blood gas analysis was normal. Coagulation parameters were within normal limits. Cranial magnetic resonance imaging revealed periventricular T2 hyperintensity and thinning of the corpus callosum. Cardiac evaluation was normal.

Initially, an intoxication was suggested, and she was treated with continuous venovenous hemodiafiltration (CVVH) and intravenous fluid containing 10% dextrose. She was fully recovered in 72 hours and amonia levels decreased to normal. Metabolic investigations were repeated during metabolic crisis. Free carnitine level was detected to be 341 µmol/L (N: 10-60) in tandem mass analysis and it was very highly elevated. Other metabolic investigations were within normal ranges. In the re-evaluation of the previous metabolic investigations, high carnitine level was noticed (140 µmol/L) in one of the tandem mass analyses. Urine organic acid analysis was normal.

CPT1a deficiency was suspected and molecular genetic analysis showed homozygous c.364_365dupAT pathogenic variant in the *CPT1A* gene. She was diagnosed with CPT1a deficiency and high-carbohydrate diet that is low in fat was commenced. She has no neurological sequelae.

Informed consent was received from the family for publication.

DISCUSSION

Here, we reported a Turkish girl patient who was diagnosed with CPT1a deficiency at 12.5 years old after an attack of hyperammonemia and altered state of consciousness. CPT1 is a long-chain fatty acid oxidation enzyme with three tissue-specific isoforms. CPT1a is liver and kidney isoform and, CPT1b and CPT1c are muscle, heart and brain isoforms respectively.[2,3] They are encoded by separate genes. Mutations in the *CPT1A* gene encoded on chromosome 11q13.3 cause CPT1a deficiency. CPT1a is the key regulatory enzyme of hepatic long-chain fatty acid beta-oxidation and CPT1a deficiency is a rare autosomal recessively inherited disorder of long-chain fatty acid oxidation with variable clinical features. CPT1a deficiency is characterized by hypoketotic hypoglycemia attacks and hepatic encephalopathy.[4] Fewer than 60 affected individuals reported.[2] It is included in newborn screening programs in some countries and asymp-

tomatic cases were reported.[5,6] However, the disorder was not included in our national newborn screening programme yet.

In CPT1a deficiency, clinical manifestations may occur when energy demands are increased such as fasting or illness. Well known clinical phenotypes are as follows: acute fatty liver of pregnancy (with CPT1a deficiency in the fetus), hepatic encephalopathy which is accompanied by hypoketotic hypoglycemia, and sudden onset liver failure. Individuals with hepatic encephalopathy are typically manifested by hypoglycemia, absent or low levels of ketones, elevated levels of liver transaminases, hyperammonemia, and elevated total carnitine levels. Between hepatic encephalopathy attacks, individuals are developmentally normal unless previous metabolic decompensation causes neurological damage.[2,3]

Key clinical features in our patient were hyperammonemia, elevated liver enzymes and absence of ketones. The association of high liver enzymes with hyperammonemia is suggestive for hepatotoxins and fatty acid oxidation disorders. Absence of ketone supported the diagnosis of one of the fatty acid oxidation disorders. In the patient, striking clinical finding leading to diagnosis of CPT1a deficiency was very high level of carnitine. Molecular genetic analysis confirmed the diagnosis. Serum ammonia levels are reported usually 100-500 µmol/L in CPT1a deficiency.[2] Ammonia level was 434 µmol/L and led to loss of consciousness in our patient. Serum glucose level was normal at admission to emergency department and she did not experience hypoglycemia in the attack course under treatment with glucose infusion. She benefited from CVVH and intravenous fluid treatment. And, long term follow up was started without neurologic sequela.

In conclusion, in the absence of skeletal muscle or cardiac symptoms, CPT1a deficiency may present similar to urea cycle disorders, other long-chain fatty acid oxidation defects, disorders of oxidative phosphorylation, disorders of gluconeogenesis and intoxication. Elevated carnitine levels with hypoketosis should alert the physician in differential diagnosis of CPT1a deficiency. This case report emphasizes the importance of reevaluating of metabolic analyses in all suspected metabolic crisis in the patients with no definite diagnosis.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Özlem Ünal Uzun;* ***Design:*** *Özlem Ünal Uzun;* ***Control/Supervision:*** *Özlem Ünal Uzun, Aynur Küçükçongar Yavaş, Mehmet Gündüz;* ***Data Collection and/or Processing:*** *Özlem Ünal Uzun, Aynur Küçükçongar Yavaş, Mehmet Gündüz;* ***Analysis and/or Interpretation:*** *Özlem Ünal Uzun, Aynur Küçükçongar Yavaş, Mehmet Gündüz;* ***Literature Review:*** *Özlem Ünal Uzun;* ***Writing the Article:*** *Özlem Ünal Uzun;* ***Critical Review:*** *Özlem Ünal Uzun, Aynur Küçükçongar Yavaş, Mehmet Gündüz.*

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