Poor Clinical Outcome In A Good Controlled Neonatal Citrullinemia Patient

İYİ KONTROLLÜ BİR NEONATAL SİTRÜLLİNEMİ OLGUSUNDA KÖTÜ KLİNİK BULGULAR

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SUMMARY

The classic citrullinemia is an autosomal recessive, metabolic disease that is caused by deficiency of the argininosuccinate synthetase. The clinical presentation is usually nonspecific and ranging from neonatal metabolic decompensation to adult onset form related to hyperammonemia and citrullinemia. Dietary protein restriction, the use of sodium benzoate arginine and phenylbutyrate are the main treatment strategies to eliminate the nitrogen and ammonia from the blood. The mechanisms responsible for the encephalopathy and central nervous system injury are not fully understood. High serum ammonia concentrations and intracerebral accumulation of glutamine in astrocytes is considered to be the major causes of the encephalopathy. Here, we described a 10 day old infant with neonatal citrullinemia without significant hyperammonemia, who had rapidly progressive clinical deterioration and elevated values of creatine kinase.

Key words: Citrullinemia, central nervous system involvement, neonate, prognosis

ÖZET

Klasik sitrüllinemi, arjininosüksinat sentetaz eksikliğinin neden olduğu, otozomal resesif geçişli bir metabolik hastalıktır. Başvurudaki klinik bulguları genellikle spesifik değildir ve neonatal metabolik dekompanzasyondan, erişkin başlangıçlı forma kadar değişkenlik gösterebilir. Kandaki nitrojen ve amonyağı elimine etmek amacıyla kullanılan sodyum benzoat, arjinin, fenilbutirat ve protein kısıtlaması esas tedavi yöntemleridir. Santral sinir sistemi hasarı ve ensefalopatinin oluşum mekanizmaları tam olarak anlaşılamamıştır. Yüksek serum amonyak konsantrasyonları ve intraserebral olarak astrositlerde glutamin birikiminin ensefalopatinin esas nedeni olduğu düşünülmektedir. Bu yazıda, ciddi hiperamonemisi olmadan hızlı bir şekilde klinik bulguları kötüleşen ve artmış kreatin kinaz değerleri saptanan 10 günlük bir infant sunulmuştur.

Anahtar sözcükler: Prognoz, santral sinir sistemi tutulumu, sitrüllinemi, yenidoğan

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The classic citrullinemia is an autosomal recessive, metabolic disease that is caused by deficiency of the Argininosuccinate Synthetase (ASS). ASS is an urea cycle enzyme and mainly synthesized in periportal hepatocytes of the liver to form argininosuccinate from the condensation of citrulline and aspartate (1,2). The incidence of Urea Cycle Disorders (UCD) is approximately 1/8200-39000 live births (3). ASS deficiency is characterized by neonatal or intermittent onset of hyperammonemia, low plasma arginine, elevated plasma and urine citrulline levels. Orotic aciduria and hyperglutaminaemia are non-specific additional abnormalities. Elevated concentrations of plasma citrulline can also be found in patients with deficiencies of argininosuccinate lyase and pyruvate carboxylase. Serum citrulline levels higher than 1000 mmol/L have been considered diagnostic for citrullinaemia (4). Diagnosis of ASS deficiency mainly relied on biochemical and enzymatic studies using liver tissue and fibroblasts (5). The ASS gene was first cloned by Bock et al, in 1983 (6). The gene coding for ASS is located on chromosome 9q34 and many mutations in ASS gene have been described which cause the classical phenotype with hyperammonemia and hypercitrullinemia (7,8).

The clinical presentation is ranging from neonatal metabolic decompensation to adult onset form related to hyperammonemia and citrullinemia. In symptomatic cases of citrullinemia, the treatment options include dietary protein restriction, substitution of arginine and essential amino acids and the use of sodium benzoate and phenylbutyrate (9). In this report, we describe rapidly progressive clinical deterioration and elevated values of Creatine Kinase (CK) in a 10 day old infant with neonatal citrullinemia who had a good metabolic control without significant hyperammonemia.

CASE REPORT

The patient was the third child of consanguineous parents and she was born after an uneventful pregnancy. The weight, height and head circumference of the patient were in normal ranges at birth. The first child of the family died on the sixth day of his life due to metabolic decompensation from hyperammonemia (1500 μg/dL) in another hospital. He did not have a specific diagnosis. The second child was a three year old boy. At the age of two years old, he was admitted to our hospital with complaints of tremor and vomiting. The diagnosis of citrullinemia was established on the basis of laboratory examinations including hyperammonemia (580 μg/dL; normal, 31-123 μg/dL), elevated serum levels of citrulline (1500 μmol/L; normal, 10–50 μmol/L) and glutamic acid (357.5 μmol/L; normal, 20-273 μmol/L), glutamine (423.3; normal, 20-500 μmol/L). He is still treated with sodium benzoate, low protein diet and substitution of arginine and essential amino acids. The present patient was immediately hospitalized soon after delivery because of family history. Physical examination was normal at birth and the ammonia level was 70 μg/dL (normal, 31-123 μg/dL). Plasma ammonia levels were followed closely and reached a peak level of 397 μg/dL at the eighth hours of life without clinical detoriation. Routine laboratory examinations revealed increased levels of serum Creatinine Phosphokinase (CK) (1579 U/L; normal, 29-168 U/L) which ranged from 1474 to 1498 U/L during the follow up. There was no acidosis or myoglobinuria and renal function tests were within normal limits. Citrullinemia was diagnosed on the basis family history and high levels of citrulline on plasma and urine samples (1700 μmol/L; normal, 10–50 μmol/L, 21350 μmol/L; normal, 0-250 μmol/L, respectively) without an argininosuccinate peak. Sodium benzoate administration, dietary protein restriction and substitution of arginine and essential amino acids were started in the first day. The plasma concentrations of ammonia ranged from 70 to 326 μg/dL during the follow up.

Inspite of the treatment and normal ammonia values, clonic convulsions started and respiratory failure developed on the 10th day of life. Muscle tonus increased with hyperreflexia in both extremities. Laboratory analysis revealed hemoglobin 11 g/dL, thrombocyte 325000/mm^3, leukocyte 6700/mm^3, C-reactive protein 1.9 mg/L (0.1-8.2 mg/L), ammonia 194 μg/dL, sodium 134 mmol/L, potassium 4.2 mmol/L, calcium 5.7 mg/dL, albumin 2.6 g/dL, magnesium 1.1 mmol/L (0.62-0.91 mmol/L), parathormone 209 pg/mL (16-67 pg/mL) and calcitonin 332 pg/mL (0-11.5 pg/mL) (Table). Magnetic Resonance Imaging (MRI) of the brain revealed symmetrical high T2

signal intensities in the cerebellum, brainstem and the white matter of both cerebral hemispheres (Figure 1 a,b). Amplitude Integrated Electroencephalography (aEEG) was recorded by Cerebral Function Monitor (CFM) and showed a pattern with the lower margin of the amplitude. Conventional EEG showed decreased rhythm amplitudes without epileptiform discharges. Despite the intensive therapy with parenteral sodium benzoate, sodium phenylacetate, fluid, glucose and lipid administration, and the slightly increased plasma concentration of ammonia; citrulline level was high (2247 μmol/L) and peritoneal dialysis was considered but the patient died at 12th day of life.

Table. Laboratory parameters of the patient during the follow up period

	Days						
	1	**2**	**3**	**5**	**8**	**10**	**11**
NH_3 (μg/dL)	70-397	326	276	70	100	194	183
CK (U/L)		1579	-	-	-	1498	1474
Ca (mg/dL)	8.9	-	9.2	-	4.9 – 6.3	6.7	7.5
PTH (pg/mL)	-	-	-	-	-	-	209
Calcitonin (pg/mL)	-	-	-	-	-	-	332
Citrulline (plasma) (μmol/L)	1700	-	-	-	-	2247	-

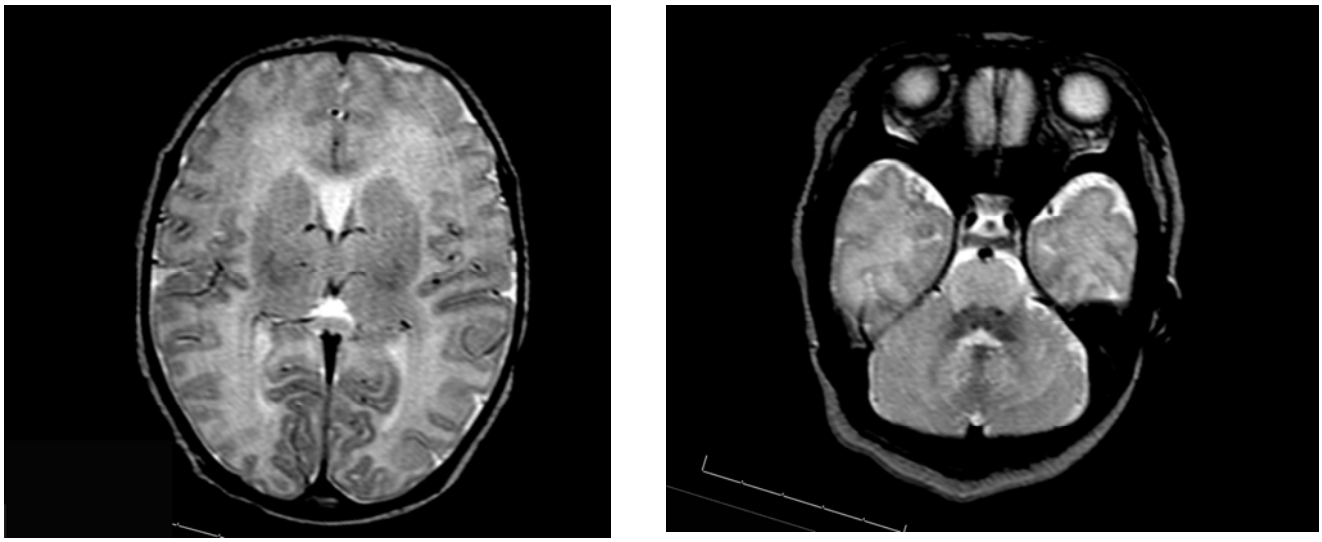

Figure 1 a,b. Supratentorial T2 weighted transverse image of the brain (a) shows symmetrical increased signal of serebral white matter of both cerebral hemispheres. Infratentorial image (b) shows increased signal of cerebellum and brainstem

DISCUSSION

Citrullinemia is a rare autosomal recessive disorder of the urea cycle and the neonates with a diagnosis of citrullinemia are prone to metabolic decompensation with hyperammonemia. The neonatal presentation of the urea cycle enzyme defects is completely nonspecific and is usually manifested by lethargy, vomiting and rapidly progress into coma (10). Dietary protein restriction, infusion of sodium benzoate and arginine are the main treatment strategies that can eliminate the nitrogen and ammonia from the blood. Generally, these treatment strategies are started soon after birth but it takes time to place catheters for infusions. On the other hand, placement of the central line causes additional stress and hence catecholamine release and proteolysis (9). Das et al reported that in patients with prenatally diagnosed UCD, the treatment of the patients with sodium benzoate via the placenta by infusing the mother with sodium benzoate shortly before the birth is safe and no side effects were observed (9). The treatment of our patient with sodium benzoate was started soon after birth and the peak level of ammonium was 397 μg/dL at eighth hour of life. We suggest that this mildly elevated levels showed the good control of our treatment despite the perinatal stress.

Although the metabolic control of the patient was good, she had rapidly progressive course with seizures, abnormal posture and respiratory failure. The brain magnetic resonance imaging at this time showed increased T2 signal intensities in the cerebral and cerebellar white matter and brainstem which may reflect to high water content of the affected tissue. There are few reports on magnetic resonance imaging in acute hyperammonemic encephalopathy due to infantile citrullinemia (11,12). The mechanisms responsible for the encephalopathy and central nervous system injury in urea cycle disorder are not fully understood. Under normal conditions, a homeostatic balance between ammonia, glutamate, and glutamine exists in the brain. In patients with urea cycle defects, hyperammonemia usually occurs during the first days of life and very high serum ammonia concentrations have been implicated as the cause of brain damage (13). But intracerebral accumulation of glutamine in astrocytes is considered to be the major cause of the encephalopathy (14,15). Magnetic resonance spectroscopy in patients with UCD shows high glutamine concentrations (16,17). Kojic et al reported a 16 year old girl with UCD, who had persistent encephalopathy long after normalization of serum ammonia (17). They demonstrated elevated levels of brain glutamine / glutamate complex by magnetic resonance single voxel spectroscopy, which later decreased toward normal on follow-up, correlating with her neurologic recovery. The correlation is poor between blood ammonia and glutamine levels. Plasma glutamine levels may also not necessarily reflect cerebral glutamine levels, which could even be higher, because glutamine is mainly produced in the brain (18). The glutamine synthetase activity is present in all parts of the brain, but it is especially high in cerebral cortex, cerebellum and hippocampus (19). The presence of a high level of ammonia results in the conversion of large amounts of glutamate to glutamine, by glutamine synthetase; which occurs mainly in the astrocytes. Acute elevated glutamine level is triggered by increased ammonia values and this elevation leads to the activation of N-Metyhyl-D-Aspartate (NMDA) receptors results in ATP depletion due to the activation of Na/K ATPase pump. All these biochemical changes result in cytotoxic edema by the accumulation of extracellular sodium and water into the cell (20). Although we could not perform magnetic resonance spectroscopy, in lights of the literature results, we suggest that probably elevated brain glutamine levels may be responsible for clinical worsening. The peak ammonia level of our patient was detected at eighth hours of age and this was probably due to perinatal stress. Although ammonia levels were in normal ranges in the follow up, clinical condition of the patient worsened at 10th day of life. We also suggest that the higher values of citrulline may also be responsible for clinical worsening of our patient.

One interesting finding in our patient was elevated CK levels. Dursun et al reported a neuroleptic malignant syndrome in an eight year old girl diagnosed with UCD that she was given haloperidol for agitation and affective disorder (21). It was reported that, patients with inborn errors of metabolism might have an increased risk for neuroleptic malignant syndrome and drugs known to be

responsible for development of neuroleptic malignant syndrome must be given cautiously (21). However, our patient did not have a history of drug use that may contribute hyperCKemia. In addition, there were no evidence to suggest rhabdomyolisis like increased blood myoglobin levels, myoglobinuria or acidosis. Catecholamines and cortisol are rapidly released following perinatal stress and that may lead proteolysis (9). One explanation for elevated CK levels may be perinatal stress. On the other hand, we detected treatment resistant hypocalcemia during follow up and simultaneously elevated CK levels. In the literature, there are several reports that describe the relationship between hypocalcemia and hyperCKemia (22,23). Ishikawa et al concluded that muscle may respond to hypocalcemia in three stages, namely homeostatic, asymptomatic hyperCKemic and myopathic stages (23). We thought that hypocalcemia in our patient may be associated with the stress induced elevated calcitonin levels which may also contribute to the elevated CK levels.

In conclusion, despite the early diagnose, and early and proper treatment neonatal citrullinemia patients might have a catastrophic clinical course. More cases are needed to explain the pathophysiology of catastrophic course in neonatal citrullinemia patients with good metabolic control.

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