Clinical Characteristics of Pediatric Patients with Urea Cycle Disorders

Kliniğimizde Üre Döngüsü Bozukluğu Nedeniyle Takipli Olan Hastaların Klinik Özelliklerinin Değerlendirilmesi

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ABSTRACT

Objective: Urea cycle disorders (UCDs) are inherited deficiencies of the enzymes or transport molecules involved in the cellular excretion of excess ammonia produced during protein metabolism. The aim of this study was to evaluate the clinical characteristics and long-term outcome of pediatric patients with UCDs.

Material and Methods: Our research was conducted between September 2020-March 2021 in Dr. Sami Ulus Maternity and Child Health Training and Research Hospital. Clinical characteristics in 16 patients with UCDs [carbamoyl phosphate synthetase I deficiency (n=1), N-acetylglutamate synthase deficiency(n=1), argininosuccinate lyase deficiency (n=4), argininosuccinate synthetase deficiency (n=4), arginase deficiency (n=2), ornithine transcarbamylase deficiency (n=2), hyperammonemia hyperornithinemia homocitrullinuria syndrome (n=2)] were defined. The term "neonatal-onset" UCD was used if symptoms occurred within 28 days of life, and "late-onset" if symptoms started after the neonatal period.

Results: Eight patients presented with acute metabolic crisis during newborn period. Core clinical phenotype in neonatal-onset UCDs included sepsis-like findings, whereas epilepsy and mental retardation was predominant in late-onset UCDs. For patients with neonatal-onset UCDs, hyperammonemia was more severe at the initial period.

Conclusion: Despite evolving treatment opportunities, still high mortality rates were found in neonatal-onset UCD. UCDs should be suspected in pediatric patients with hyperammonemia and metabolic investigations should be performed immediately to enlighten diagnosis. Neonatal-onset UCD usually present with symptoms of acute hyperammonemia, while moresubtle neurological manifestations are frequent initial findings in the late onset UCD.

Key Words: Hyperammonemia, Neonate, Inborn urea cycle disorders

ÖZ

Amaç: Üre döngüsü bozuklukları (ÜDB'leri), protein metabolizması sonucunda üretilen amonyağın hücresel atılımında yer alan enzimlerin veya taşıyıcı moleküllerinin kalıtsal eksikliklerinden kaynaklanan doğumsal metabolik hastalıklardır. Bu çalışmanın amacı, bölümümüzde takipli olup, ÜDB olan pediatrik yaş grubundaki hastaların klinik özelliklerini ve uzun dönem sonuçlarını değerlendirmektir.

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Gereç ve Yöntemler: Araştırmamız Eylül 2020-Mart 2021 tarihleri arasında, Dr. Sami Ulus Kadın Doğum ve Çocuk Sağlığı ve Hastalıkları Eğitim ve Araştırma Hastanesi'nde gerçekleştirildi. ÜDB olan 16 hastada [karbamoilfosfatsentetaz I eksikliği (n=1), N-asetil glutamate sentaz eksikliği(n=1), arginino süksinat liyaz eksikliği (n=4), argininosüksinat sentetaz eksikliği (n=4), arginaz eksikliği (n=2), ornitin transkarbamilaz eksikliği (n=2), hiperamonyemi-hiperornitinemi-homositrülinüri sendromu (n=2)] klinik özellikler geriye yönelik olarak tarandı. Semptomlar yaşamın 28 günü içinde ortaya çıkmış ise "neonatal başlangıçlı ÜDB" terimi, semptomlar yenidoğan döneminden sonra başladı ise "geç başlangıçlı ÜDB" terimi kullanıldı.

Bulgular: Sekiz hasta yenidoğan döneminde akut metabolik kriz ile başvurmuştu. Neonatal başlangıçlı ÜDB'lerde temel klinik fenotip sepsis benzeri bulguları içerirken, geç başlangıçlı ÜDB'lerde epilepsy ve mental retardasyon baskındı. Neonatal başlangıçlı ÜDB olan hastalarda, başlangıç döneminde hiperamonyeminin daha şiddetli olduğu gözlemlendi.

Sonuç: Gelişmekte olan tedavi yöntemlerine rağmen, neonatal başlangıçlı ÜDB'lerde mortalite oranları halen yüksek olarak seyretmektedir. Neonatal başlangıçlı ÜDB'ler genellikle akut hiperamonyemi semptomları ile kendini gösterirken, nörolojik belirtiler geç başlangıçlı ÜDB'de sıklıkla başlangıç belirtisi olarak karşımıza çıkmaktadır. Hiperamonyemisi olan çocuk hastalarda ÜDB'lerden şüphelenilmeli ve tanıyı aydınlatmak için metabolik incelemeler ivedilikle yapılmalıdır.

Anahtar Sözcükler: Hyperammonemia, Yenidoğan, Doğuştan üre döngüsü bozuklukları

INTRODUCTION

Urea cycle disorders (UCDs) are inherited metabolic disorders (IEMs) related with the defects in one of the enzymes or transporters involved in the detoxification of ammonia by conversion to non-toxic urea. UCDs are defects of breakdown of amino acids due to various genetic variations (1,2).

The involved enzymes are carbamoyl phosphate synthetase 1 (CPS1), ornithine transcarbamylase (OTC), argininosuccinate synthetase (ASS), argininosuccinate lyase (ASL) and arginase (ARG1), the mitochondrial ornithine-citrulline antiporter (ORC1) that leads to hyperornithinemia-hyperammonemia-homocitrullinuria (HHH) syndrome, the enzyme N-acetylglutamate synthase (NAGS) that activates CPS1 and citrin (mitochondrial aspartate-glutamate antiporter) (1,2). The deficiencies of these enzymes cause subtypes of UCDs including CPS1 deficiency, OTC deficiency, ASS deficiency, ASL deficiency, HHH syndrome, NAGS deficiency and citrine deficiency. All UCDs are inherited autosomal recessively, while OTC deficiency is X-linked. Toxic substances, mainly ammonia accumulate in blood in UCDs and may cause serious organ damage, including mainly the nervous system and the liver, or even death. The presentation may be early or late onset, that may determine the prognosis of disease (3,4).

The aim of this study was to document the characteristics and outcome of pediatric patients with UCDs that were diagnosed in our clinic.

MATERIAL and METHODS

Sixteen patients from different families, that were diagnosed and being followed-up Dr. Sami Ulus Maternity and Child Health Training and Research Hospital between September 2020 – March 2021 were included in the study. Data of patients including age, sex, subtype of UCD, age of presentation, genetic variants and clinical findings were collected from patient files. The term "neonatal-onset" UCD defined that symptoms occurred during the first 28 days of life, and "late-onset" defined symptoms starting afterwards.

Informed consent was obtained from parents of each patient included in the study. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki The study was approved by the ethics commitee of Ankara City Hospital (1099/16.09.2020).

RESULTS

Clinical characteristics in 16 patients with UCD; including CPS (n=1), NAGS (n=1), ASL (n=4), ASS (n=4), ARG1 (n=2), OTC (n=2) deficiencies, and HHH syndrome (n=2) were defined. Male to female ratio was 8 / 8. Parental consanguinity was present in 13 out of 16 patients. Eight out of 16 patients presented with acute metabolic crisis during newborn period. Age of presentation varied between 2 to 33 days. The main clinical phenotype in neonatal-onset UCD included sepsis-like neonatal crisis revealed in patients within 28 days after birth, and vomiting and coma were frequently reported. For patients with neonatal-onset UCD, hyperammonemia was more prominent during the first presentation of the disease. Initial levels of ammonia varied between 253-2460 µmol/L. Seven out of 8 neonatal onset patients required extracorporeal detoxification, among which 2 patients received peritoneal dialysis (PD), and 5 received continous venovenous hemodiafiltration (CVHH). The mortality rate in neonatal onset cases was 50%. While two patients with neonatal onset UCD showed normal development and were stable, 2 patients had intellectual disability and developmental delay, among the surviving 4 patients (50%) (Table I).

Among late-onset patients, epilepsy and intellectual disability were predominant, emerging more than 28 days after birth. Five out of 8 late-onset patients had parental consanguinity. Age of presentation varied between 33 days to 10 years. Initial symptoms were vomiting, developmental delay, encephalopathy, behavioural changes and hepatic failure. Initial ammonia levels varied between 51 to 273 µmol/l. Only one patient required extracorporeal detoxification that was

Table I: Clinical characteristics of patients involved in the study.

	Patient (Gender)	Diagnosis	Parental consanguinity	Age at admission	Presenting symptoms	Initial ammonia (µmol/L)*	Dialysis mode	Mutation	Outcome
Neonatal onset	1 (M)	ASSD	+	3 d	Vomiting Coma	495	PD	Homozygous ASS1 c.1085G>T	S: 6 y; normal development
	2 (F)	ASSD	+	3 d	Coma	1293	CVVH	NA	D: 21 d
	3 (F)	CPS1D	+	2 d	Vomiting Coma	1371	PD	Homozygous CPS1 c.622_711delExon7	S: 5 y; intellectual disability
	4 (F)	NAGSD	+	6 d	Coma Septic findings	1418	CVVH	Homozygous NAGS c.1450C>T	S: 18 mo; moderate developmental delay
	5 (F)	ASLD	+	6 d	Vomiting Coma	1404	CVVH	Homozygous ASL c.436C>T	D: 15 d
	6 (M)	ASLD	+	4 d	Coma	2460	CVVH	Homozygous ASL c.446+1G>A	D: 20 d
	7 (M)	ASLD	+	3 d	Coma	2551	CVVH	Homozygous ASL c.556C>T	D: 5 d
	8 (M)	HHH	+	2 d	Asymptomatic (Due to family history)	253	PD	Homozygous SLC25A15 c.692A>T	S: 2 y; stable course
Late onset	9 (M)	ASSD	-	33 d	Vomiting	397	PD	Compound heterozygous ASS1 c.814C>T / c.970 + 5G>A	S: 12 mo
	10 (M)	ASSD	+	10 m	Vomiting Developmental delay	74	-	Homozygous ASS1 c.1085G>T	S: 4 y; mild intellectual disability
	11 (F)	OTCD	-	3.5 y	Vomiting	273	-	Heterozygous OTC c.563G>T	S: 5y; normal growth and development
	12 (F)	OTCD	-	5 y	Recurrent encephalopathy	203	-	Heterozygous OTC C:67C>T	S: 7 y; normal growth and development
	13 (F)	ARGD	+	14 y	Epilepsy Mental retardation	154	-	Homozygous ARG1 c.58-3C>G	S: 16 y; stable course
	14 (F)	ARGD	+	2 y	Status epilepticus Hepatic failure	51	-	Homozygous ARG1 c.703_707delGGACTinsAGACTGGACC	S: 3.5; cessation of hepatic failure episodes
	15 (M)	HHH	+	17 y	Epilepsy	155	-	Homozygous SLC25A15 c.535C>T	S: 18 y; stable course
	16 (M)	ASLD	+	11 y	Epilepsy ADHD	120	-	Homozygous ASL c.370 T>A	S: 16 y; stable course

performed by PD. Six out of eight patients showed stable progress and normal development. Only 1 patient among late-onset patients showed mild intellectual disability (Table I).

Diagnoses of all patients were confirmed with molecular genetic analyses. Genetic variants are shown in Table I.

DISCUSSIONS

UCDs are inherited metabolic disorders caused by the defects of one of the enzymes related to urea cycle. The overall incidence of UCDs is nearly 1:35.000 births, and they are all inherited autosomal recessively other than OTC deficiency which is X-linked. Hyperammonemia that is toxic to the central nervous system (CNS) accumulates in bloodstream in UCDs (3,4).

Symptoms of UCDs may occur abruptly, or may manifest in a more chronic way, especially in older ages. Acute symptoms are usually triggered by catabolic events or protein intake. Clinical features are typical in neonatal cases, where enzyme deficiency is complete, which present as hyperammonemic episodes soon after birth with high mortality, and patients experience severe neurological sequela and recurrent hyperammonemic episodes (2). Partial deficiencies present with variable clinical presentations and are later onset, usually present as recurrent attacks of vomiting or encephalopathy. Hepatic and psychiatric findings have been reported. Some specific symptoms may also present, e.g., hair shaft abnormalities (trichorrhexis nodosa) in ASL deficiency and progressive spastic diplegia in ARG1 deficiency and HHH syndrome (5,6).

The initial presentations of our patients were also in accordance with the literature. The neonatal cases mainly presented as hyperammonemic encephalopathy and vomiting, while late-onset patients showed variable manifestations related with the subtype of underlying UCD (e.g. intellectual disability, spasticity, growth retardation) (7). According to the study of Dorum et al. (7), neonatal-onset patients mostly presented as an acute metabolic attack including sespsis like findings, feeding disorder and coma, while later onset patients had chromic symptoms.

Hyperammonemia is an indicator of nitrogen detoxification and is a hallmark for many UCDs. Since the length and quantity of hyperammonemia are related with CNS damage, early diagnosis and treatment is essential. Protein intake should be stopped immediately in a hyperammonemic patient and intravenous dextrose infusion should be given along with nitrogen scavenger drugs (if ammonia level is above 100 umol/L). This is valid for UCDs other than citrin deficiency, as high glucose and protein restriction may worsen the clinical picture (5). Dialysis should be performed when ammonia levels are higher than 500 µmol/L or when there is no decrease in ammonia levels within four hours after initiation of medical therapy. Long-term management of UCDs consists of low protein diet (other than citrin deficiency) and nitrogen scavengers (5). Liver transplantation is also a treatment option for many UCDs, and is curative since it allows cessation of the low-protein diet, but does not improve neurological sequelae (8). Our patients were also treated in accordance with the mentioned guidelines in the literature. Despite appropriate treatment, neonatal-onset cases had mostly poor prognosis.

Dorum et al. (7) have retrospectively analyzed data of 12 patients with UCD and reported that neonatal-onset patients had poor prognosis when compared to later-onset UCD patients. The authors have emphasized the importance of early diagnosis to be the most important measure to improve long term survival. Similiar to findings of Dorum et al. (7), in our patient series, patients with highest ammonia levels also had died in the early course of disease. Within our patient group, ammonia levels ranged between 51 to 2460 µmol/L, and neonatal-onset cases demonstrated higher levels. Due to this condition, 85% of neonatal-onset cases required extracorporeal detoxification.

Bachman has analyzed the outcome of 88 patients with UCDs (9). The author has concluded that, there was an increased risk of intellectual disability in the neonatal-onset group despite extensive treatment, and none of the patients whose plasma ammonia levels were higher than 300 µmol/l initially, had a normal cognitive outcome. Similarly, in our patient group, poor outcome was observed in the neonatal-onset group where ammonia levels were severely increased (above 1000 µmol/L). Our findings also support the fact that hyperammonemia should be detected at the earliest period and treated immediately to prevent irreversible neurological damage and deaths.

Despite the treatment opportunities, mortality rates are still high in neonatal-onset UCDs-around 60%. In our series of patients mortality rate was similar to the rate reported in the literature (%50 among neonatal cases) (8,10). A meta-analysis that has reviewed the observational studies on UCDs, that were published over more than 35 years, has concluded that all UCDs, except female OTCs, have high risks for early onset disease, and neonatal death except for ASLD. It has also been underlined that no improvement of survival was observed over more than three decades (11). In accordance with the findings of this study, our study population also shows that, despite evolving treatment opportunities, mortality among UCD patients is still high, especially among early onset patients, and the underlying subtype of UCD is an important determinant of prognosis.

CONCLUSION

UCDs should be suspected in neonates with hyperammonemia and metabolic tests including ammonia level should be performed immediately to enlighten underlying diagnosis. Although neurological manifestations are reported to be more diagnostic in the late onset UCD, severe hyperammonemia may

cause irreversible neurological damage in the newborn period, and early diagnosis and treatment is essential for prevention.

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