PHENOTYPIC CHARACTERISTICS AND OUTCOMES OF LATE-ONSET UREA CYCLE DISORDERS

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Urea cycle disorders (UCD) are characterized by elevated blood ammonia levels due to deficiencies in enzymes essential for urea metabolism. Early diagnosis and treatment reduce mortality and sequelae. Objective: To describe the phenotypic characteristics and treatment outcomes of late-onset UCD from 2010 to September 2021. Results: 32 patients from 27 families with a median age of onset of 30 months old (range: 2-180 months). 33.3% of patients had a relevant family history. Reasons for medical consultation included vomiting, fatigue/ poor appetite, and lethargy. Clinical presentation upon admission: 68.8% had impaired consciousness, 75% exhibited vomiting and poor appetite, 15% experienced seizures, and 6.2% presented with muscle tone disorders. Laboratory findings showed hyperammonemia in 93.8% of cases, with elevated lactate, increased liver enzymes, and decreased prothrombin time in 87.5% of patients. Treatment with ammonia-lowering medications, hemodialysis, and glucose infusion successfully saved 87.5% of patients. Conclusion: Blood ammonia testing is essential in patients with altered consciousness, elevated liver enzymes, and decreased prothrombin time. Glucose infusion, ammonia-lowering medications, and hemodialysis demonstrate favorable outcomes.

Keywords: Urea cycle disorders.

I. INTRODUCTION

Urea cycle disorders (UCD) are inborn errors of metabolism characterized by elevated blood ammonia levels due to deficiencies in enzymes essential for urea metabolism.

Urea cycle disorders are rare conditions. In the United States, the incidence is approximately 1/35,000 live births.[1] According to research by Uchino et al., in Japan, the incidence is 1/50,000 live births.[2]

Clinically, UCDs are classified into two main forms: neonatal-onset occurring during the neonatal period and late-onset occurring after the neonatal period. Late-onset UCDs present with nonspecific clinical manifestations and progress rapidly with severe outcomes.[3,4] The disease is often diagnosed late, resulting in mortality or severe sequelae.[3,5] Even in previously diagnosed children, acute episodes may occur due to triggering factors such as infections or treatment discontinuation.

In Vietnam, there have been few studies on late-onset urea cycle disorders.[6] Therefore, with the aim of facilitating early diagnosis and optimal management for patients with late-onset UCDs, we conducted this study to describe the phenotypic characteristics and treatment efficacy of late-onset urea cycle disorders.

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II. MATERIALS AND METHODS

1. Subjects

32 patients diagnosed and managed at the Vietnam National Children's Hospital from 2010 to September 2021.

Inclusion criteria

Patients with urea cycle disorders according to the criteria of the World Rare Disease Association[7]:

- Infants or young children with episodes of vomiting, lethargy, coma, or psychomotor developmental delay, muscle tone disorders.
- Blood ammonia concentration elevated above 100 µmol/l in children beyond the neonatal period.
- Normal blood glucose and normal anion gap.
- Plasma amino acid profile and urinary organic acid analysis showing changes consistent with urea cycle disorders.
- Enzyme activity quantification and genetic analysis are definitive diagnostic tests for specific types of urea cycle disorders.

Exclusion criteria

Patients with incomplete information were not selected.

2. Methods

Case series study was conducted at the Vietnam National Children's Hospital from January 2019 to December 2021. Clinical and laboratory characteristics including age, gender, family history, consciousness upon admission assessed according to coma scale, neurological signs: increased/decreased muscle tone, assessment of respiratory failure, blood ammonia, blood gases, blood glucose, blood lactate, SGOT, SGPT, complete blood count, basic coagulation, genetic analysis results.

Blood amino acid and urinary organic acid analysis: results of blood amino acid and urinary organic acid analysis. Acylcarnitine quantification using Tandem Mass technique: Each patient had a drop of blood collected on Guthrie filter paper, ensuring complete saturation of the circular filter paper, and allowed to dry naturally at room temperature for 4 hours. Patient name, age, clinical signs, and laboratory tests were recorded on pre-printed paper forms. Specimens were sent to the Biochemistry Department for acylcarnitine quantification using Tandem Mass technique, a double mass spectrometry method quantifying several acylcarnitines and amino acids in dried blood spot samples on the LC-MS/MS 8040 system from Shimadzu. Other tests were performed at the Biochemistry Department, National Children's Hospital.

Data were processed using SPSS 22.0 statistical software. All research information was retrieved from medical records, information was kept confidential, and there was no intervention in patient treatment. The study was conducted in accordance with all principles of research ethics.

III. RESULTS

32 patients from 27 families met the study criteria. The age of onset varied from 2 months to 15 years old. 33% had a family history of similar disease or diagnosed urea cycle disorders. The incidence was higher in females than males (table 1). Common reasons for hospital admission were vomiting, poor appetite, and altered consciousness. Upon admission, 68.8% presented with unconsciousness, 75% with vomiting and poor appetite, 15% with seizures, and 6.2% with dystonia (table 2). 93.8% of patients had hyperammonemia with 81.2% showing mild to moderate elevation. Elevated lactate, increased liver enzymes, and decreased prothrombin time were observed in 87.5% of cases. 37.5% had mild to moderate metabolic acidosis (table 3). Hemodialysis was performed on 4 patients with high and very high levels of hyperammonemia. Four patients passed away due to circulatory/respiratory failure and deep coma (table 4).

1. Demographics of the study group

Table 1. Characteristics of the study group

Characteristics (n = 32)		Value	
Onset age (months)		Median: 30 months old Min – Max: 2 – 180 months	
Gender and family history		n	%
Gender	Male	10	31.3
	Female	22	68.7
Family history (n = 27)	Affected siblings	7	25.9
	Affected relatives	2	7.4
	None	18	66.7

2. Phenotypic characteristics of late-onset urea cycle disorders

Table 2. Clinical characteristics

Clinical characteristics (n = 32)		n	%
Reason for hospitalization	Alter	21	65.6
	Vomiting	24	75
	Poor appetie	21	65.6
Consciousness condition	A	11	34.4
	V	14	43.8
	P	7	21.9
Vomiting		24	75
Poor appetite		24	75
Respiratory failure		2	6.2
Dystonia		2	6.2
Seizures		5	15.6

Table 3. Laboratory characteristics

Laboratory characteristics		n	%
Hyperammonemia (µmol/l)	Total	30	93.8
	Mild (150 – 250)	9	28.1
	Moderate (251 – 500)	17	53.1
	High (501 – 1000)	3	9.4
	Severe (trên 1000)	1	3.1

Laboratory characteristics		n	%
Hypertransaminase (UI/L)	Total	28	87.5
	Elevated GOT Median (Min – Max)	23 176 (53 – 3486)	71.8
	Elevated GPT Median (Min – Max)	28 241 (40 – 1987)	87.5
Hypoglycemia		0	0
Lactat elevation (nmol/L)	Total	28	87.5
	High (> 6 mmol/l) Median (Min-Max)	4 8.0 (6.8 – 14.1)	12.5
	Moderate (2 – 6 mmol/l) Median (Min – Max)	24 3.66 (2.3 – 5.2)	75
Metabolic acidosis	Total	12	37.5
	Mild (pH: 7.25 – 7.35) Median (Min – Max)	8 7.29 (7.25 – 7.32)	25
	Moderate (pH: 7.15 - <7.25) Median (Min – Max)	3 7.19 (7.15 – 7.20)	9.4
	Severe (pH: < 7.15)	0	0
Ketouria		0	0
Elevated WBC (> 10,000 cells/ml)		13	40.6
Decreased prothrombin time (%) Median (Min – Max)		28 45 (12 – 79)	87.5

3. Treatment methods and outcomes

Table 4. Treatment methods and outcomes

Treatment methods	n	%
Glucose infusion	26	81.2
L-carnitine	29	90.6
L-Arginine	30	93.8
Sodium Benzoat	20	62.5
Hemodialysis	4	12.5
Outcomes		
Deceased	4	12.5
Survive	28	87.5

IV. DISCUSSION

Our study collected data from 32 patients who met the research criteria. The age of onset varied widely, with the earliest being 2 months old and the latest 180 months old with a median of 32 months old. This demonstrates that acute episodes of inborn urea cycle disorders can occur at any age, from a few days old to older children. This characteristic should be noted to avoid missing diagnoses in older children due to the misconception that inborn metabolic disorders only manifest in the neonatal period.

Most patients (66.7%) had no family history related to the disease. Only 33.3% had siblings or relatives with similar conditions or unexplained deaths. Identifying a family history of suspected or confirmed urea cycle disorders is extremely valuable for clinicians when approaching patients with genetic diseases in general and urea cycle disorders in particular. However, vigilance should be maintained even in cases without remarkable family history.

Common reasons for hospitalization included unconsciousness (65.6%), vomiting (75%), and fatigue (65.6%). These presenting complaints can easily lead to misdiagnosis upon initial admission being confused with gastrointestinal or neurological infections. Therefore, clinicians need to conduct thorough examinations combined with detailed family history inquiries.

Unconsciousness was also a common symptom with a rate of 65.6%. However, the level of consciousness in this group was typically drowsiness corresponding to level V at 43.8%. Other symptoms were vomiting (75%), poor appetite (65.6%), seizures (15.6%) and muscle tone disorders (6.2%). Thus, the prominent clinical feature of acute episodes in late-onset urea cycle disorders is acute encephalopathy syndrome: poor feeding/ appetite vomiting, lethargy, seizures which can appear at any age. Therefore, plasma ammonia testing is necessary to be routinely performed for all patients with unconsciousness.

Laboratory characteristics of acute episodes commonly included hyperammonemia (93.7%). Two cases without elevated ammonia were children from families with previously diagnosed urea cycle disorders who had undergone genetic analysis. Coagulation disorders with decreased prothrombin time, elevated transaminases and increased lactate were also common findings, present in 87.5% of cases. Additionally, no change in blood glucose or urinary ketones was observed in aforementionned cases. The main laboratory findings were consequences of liver damage such as decreased prothrombin time and elevated liver enzymes. This is consistent with previous studies.[8,9]diagnosed with UCD at a single metabolic referral center between 1979 and 2017, were included. Clinical and laboratory data were retrieved retrospectively from hospital records. Results Classical citrullinemia was the most common type of UCD; citrin deficiency and carbamoyl phosphate synthase 1 deficiency (CPS1D Therefore, patients with elevated liver enzymes and decreased prothrombin ratio should be tested for blood ammonia and screened for urea cycle disorders.

The degree of hyperammonemia was predominantly in the moderate range (251-500 µmol/L) accounting for 53.1%. Only 3/32 (9.4%) children had high levels of hyperammonemia and 1/32 (3.1%) had very high levels. In cases with mild hyperammonemia, consciousness levels were typically A-V. Notably, when ammonia levels were high or very high, patients presented with consciousness level P. A relationship between the degree of hyperammonemia and the severity of impaired consciousness was observed: higher ammonia levels corresponded

with worse consciousness states. Decreased prothrombin ratio was observed in 87.5% of caseswith a median prothrombin ratio of 45%. According to Elena et al.'s 2013 study in Spain, the median prothrombin ratio was 60%.[3] This result is higher than our study. The difference may be due to patients presenting to our facility at later stages, when liver damage was more severe, leading to a more significant decrease in prothrombin ratio. Leukocytosis was observed in 16/32 (50%) cases and leukopenia in 2/32 (6.3%) cases. Leukocytosis/leukopenia is commonly found in infectious diseases, which are also known triggers for acute episodes according to the literature. This suggests that in late-onset forms, infection is a common precipitating factor for acute episodes.

Patients in our study were treated according to international metabolic disorder protocols.[10] Fluid therapy was administered to 26/32 (81.3%) children with late-onset disease. This measure helps control protein intake and ensures energy requirements to interrupt the body's catabolic reactions. 29 (90.6%) children received sodium benzoate, a nitrogen scavenger which helps reduce blood ammonia levels. Hemodialysis is a method that rapidly eliminates ammonia from the blood.[11] In our study, the hemodialysis rate was 12.5%, performed on all 4 patients with high and very high levels of hyperammonemia. After treatment, 28 patients survived and 4 patients passed. These 4 patients were in coma upon admission with high and very high blood ammonia levels. The severity of hyperammonemia or the rate of ammonia elimination affects treatment outcomes. Picca et al demonstrated that patients with blood ammonia concentrations exceeding 1000µmol/L have a very high mortality rate.[12] Therefore, early detection of the disease before patients develop high or very high hyperammonemia is crucial for survival.

V. CONCLUSION

Late-onset urea cycle disorders typically present with diverse gastrointestinal and neurological symptoms. For early diagnosis, routine blood ammonia testing is essential for patients with unconsciousness, elevated liver enzymes and decreased prothrombin time. Emergency treatment with ammonia-lowering medications and hemodialysis is critical for patient survival.

Acknowledgment and conflict of interest declaration

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REFERENCES

1. Summar ML, Koelker S, Freedenberg D, et al. The incidence of urea cycle disorders. *Mol Genet Metab*. 2013;110(1-2):179-180. doi:10.1016/j.ymgme.2013.07.008

2. Uchino T, Endo F, Matsuda I. Neurodevelopmental outcome of long-term therapy of urea cycle disorders in Japan. *J Inherit Metab Dis*. 1998;21 Suppl 1:151-159. doi:10.1023/a:1005374027693

3. Martín-Hernández E, Aldámiz-Echevarría L, Castejón-Ponce E, et al. Urea cycle disorders in Spain: an observational, cross-sectional and multicentric study of 104 cases. *Orphanet J Rare Dis*. 2014;9:187. doi:10.1186/s13023-014-0187-4

4. Wells DL, Thomas JB, Sacks GS, et al. Late-onset urea cycle disorder in adulthood unmasked by severe malnutrition. *Nutr Burbank*

Los Angel Cty Calif. 2014;30(7-8):943-947. doi:10.1016/j.nut.2013.12.011

5. Summar ML, Dobbelaere D, Brusilow S, et al. Diagnosis, symptoms, frequency and mortality of 260 patients with urea cycle disorders from a 21-year, multicentre study of acute hyperammonaemic episodes. *Acta Paediatr Oslo Nor 1992*. 2008;97(10):1420-1425. doi:10.1111/j.1651-2227.2008.00952.x

6. Nguyen Thanh Hong. *Nghien cuu dac diem dich te hoc lam sang va ket qua dieu tri benh roi loan chuyen hoa chu trinh ure o tre em*. Hanoi Medical University. 2015.

7. Ah Mew N, Simpson KL, Gropman AL, et al. Urea Cycle Disorders Overview. In: Adam MP, Feldman J, Mirzaa GM, Pagon RA, Wallace SE, Amemiya A, eds. *GeneReviews®*. University of Washington, Seattle; 1993. Accessed April 11, 2025. http://www.ncbi.nlm.nih.gov/books/NBK1217/

8. Saritaş Nakip Ö, Yıldız Y, Tokatlı A. Retrospective evaluation of 85 patients with urea cycle disorders: one center experience, three new mutations. *J Pediatr Endocrinol Metab JPEM*. 2020;33(6):721-728. doi:10.1515/jpem-2019-0413

9. Jalan A, Häberle J, Kudalkar K, et al. Survival and outcome of patients with urea cycle disorders: a single-center experience. *Perinatology*. 2016;17(3):110-119. doi:10.5167/uzh-132060

10. Häberle J, Burlina A, Chakrapani A, et al. Suggested guidelines for the diagnosis and management of urea cycle disorders: First revision. *J Inherit Metab Dis*. 2019;42(6):1192-1230. doi:10.1002/jimd.12100

11. Arbeiter AK, Kranz B, Wingen AM, et al. Continuous venovenous haemodialysis (CVVHD) and continuous peritoneal dialysis (CPD) in the acute management of 21 children with inborn errors of metabolism. *Nephrol Dial Transplant Off Publ Eur Dial Transpl Assoc - Eur Ren Assoc*. 2010;25(4):1257-1265. doi:10.1093/ndt/gfp595

12. Picca S, Dionisi-Vici C, Abeni D, et al. Extracorporeal dialysis in neonatal hyperammonemia: modalities and prognostic indicators. *Pediatr Nephrol Berl Ger*. 2001;16(11):862-867. doi:10.1007/s004670100702