UREA CYCLE DISORDERS AT A TERTIARY PEDIATRIC CENTER IN VIETNAM OVER 20 YEARS: SPECTRUM, PHENOTYPE, GENOTYPE, AND OUTCOMES

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Background:
Urea cycle disorders (UCDs) are rare but potentially fatal metabolic diseases. Advances in diagnostics have improved recognition in Vietnam, enabling analysis of clinical characteristics and outcomes. This study aimed to describe the spectrum, phenotypes, genotypes, and outcomes of UCDs over two decades at a tertiary pediatric center.

Methods:
This case series study was conducted from 2005 to 2024 at a tertiary pediatric center in Vietnam. A total of 117 patients diagnosed with UCDs were included. Dried blood spot amino acids and acylcarnitine analysis was performed using LC-MS/MS. Plasma amino acides was analysed using HPLC; urinary organic acides was analysed using GC/MS and molecular testing using next-generation sequencing. Phenotypic and genotypic data were reviewed, and outcomes were assessed based on survival, neurodevelopment, and disease progression.

Results:
The cohort included 60 patients with ornithine transcarbamylase (OTC) deficiency, 19 patients with citrullinemia type I, 3 patients with argininosuccinic aciduria, 6 with HHH syndrome, 4 patients with CPS1 deficiency, and 25 unclassified cases. Genetic testing was performed in 60% of patients, with pathogenic variants identified in the genes *OTC*, *ASS1*, *CPS1*, *ASL*, and *SLC25A15*. Neonatal-onset and late-onset phenotypes were observed in 51% and 49% of cases, respectively. Presenting symptoms commonly included hyperammonemia, vomiting, lethargy, and seizures. Among 56 patients with OTC deficiency, five phenotypes were identified: neonatal-onset males (41%), late-onset males (12.5%), neonatal-onset females (2%), late-onset females (37.5%), and asymptomatic females (7%). The mean age of onset was 7.3 years for late-onset males and 3.5 years for females. Ammonia levels varied significantly by phenotype ($p < 0.05$), correlating with age at onset. At last follow-up, the ages of surviving patients ranged from 2.5-17 years (late-onset females), 6-15 years (late-onset males), and 5-12 years (neonatal-onset males). Neonatal-onset males had the highest early mortality rate (64.7%) and universally poor

neurodevelopmental outcomes. In contrast, late-onset phenotypes demonstrated more favorable prognoses, especially with early diagnosis and sustained metabolic control.

Conclusion:
UCDs in Vietnamese children display broad clinical and genetic heterogeneity. Neonatal-onset OTC deficiency has the poorest prognosis. Early diagnosis, molecular confirmation, and individualized care are essential, while liver transplantation and gene therapy may offer long-term solutions for severe cases.