Plasma Glutamine and Ammonia Dynamics as Predictors of Hyperammonemic Crisis in Urea Cycle Disorders: A Retrospective Study Stratified by Onset Type

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Background:

Urea cycle disorders (UCDs) are inherited metabolic diseases caused by enzymatic deficiencies in the hepatic urea cycle, resulting in the accumulation of neurotoxic ammonia (NH_3). Hyperammonemic crisis (HAC) is a life-threatening complication, especially in neonatal-onset UCD, and is associated with poor neurological outcomes when plasma NH_3 levels exceed 600 μg/dL. Although current guidelines recommend maintaining plasma glutamine (Gln) levels below 1000 μmol/L, reliable prediction of HAC remains a major clinical challenge.

Objective:

To determine whether dynamic changes in plasma NH_3 and Gln concentrations can predict HAC in UCD patients under chronic management, and to assess whether these predictive patterns differ by onset type (neonatal vs. late-onset) and by timing before HAC.

Methods:

We retrospectively analyzed 18 UCD patients (9 neonatal-onset [NO], 9 late-onset [LO]) followed at a single center from 2014 to 2024. Plasma NH_3 and Gln levels were collected during routine outpatient visits and within 90 days before HAC episodes (defined as NH_3 ≥150 μg/dL). We calculated the changes in NH_3 and Gln (ΔNH_3, ΔGln) over two intervals: from 61–90 to 31–60 days, and from 31–60 to 14–30 days before HAC. Associations with subsequent HAC risk were assessed using generalized linear mixed models (GLMMs).

Results:

The interactions of both ΔGln and ΔNH_3 with onset type were statistically significant ($p < 0.01$), indicating differential effects on HAC risk between NO and LO groups.

In the NO group, both ΔGln and ΔNH_3 from 31–60 to 14–30 day interval before HAC were clearly sassociated with HAC risk. An increase of 400 μmol/L in ΔGln was associated with a 45.0% probability of HAC, while an 80 μg/dL increase in ΔNH_3 corresponded to a 22.5% probability. In contrast, changes during the earlier period (61–90 to 31–60 days prior) were not predictive. No significant predictive associations were observed in the LO group during either interval.

Conclusion:

In neonatal-onset UCD, increasing trends in plasma Gln and NH_3 levels within 31–60 days prior to HAC may serve as early indicators of impending crisis, supporting the clinical utility of longitudinal biomarker monitoring. The absence of such patterns in late-onset UCD suggests distinct pathophysiological mechanisms and highlights the need for alternative risk assessment strategies in this subgroup.