Infectious Precipitants of Acute Hyperammonemia Are Associated with Indicators of Increased Morbidity in Patients with Urea Cycle Disorders

Peter J. McGuire, MS, MD[1], Hye-Seung Lee, PhD[2], members of the Urea Cycle Disorders Consoritum,* and Marshall L. Summar, MD, PhD[3]

Objective To prospectively characterize acute hyperammonemic episodes in patients with urea cycle disorders (UCDs) in terms of precipitating factors, treatments, and use of medical resources.

Study design This was a prospective, longitudinal observational study of hyperammonemic episodes in patients with UCD enrolled in the National Institutes of Health–sponsored Urea Cycle Disorders Consortium Longitudinal Study. An acute hyperammonemic event was defined as plasma ammonia level >100 μmol/L. Physician-reported data regarding the precipitating event and laboratory and clinical variables were recorded in a central database.

Results In our study population, 128 patients with UCD experienced a total of 413 hyperammonemia events. Most patients experienced between 1 and 3 (65%) or between 4 and 6 (23%) hyperammonemia events since study inception, averaging fewer than 1 event/year. The most common identifiable precipitant was infection (33%), 24% of which were upper/lower respiratory tract infections. Indicators of increased morbidity were seen with infection, including increased hospitalization rates (P = .02), longer hospital stays (+2.0 days; P = .003), and increased use of intravenous ammonia scavengers (+45%-52%; P = .003-.03).

Conclusion Infection is the most common precipitant of acute hyperammonemia in patients with UCD and is associated with indicators of increased morbidity (ie, hospitalization rate, length of stay, and use of intravenous ammonia scavengers). These findings suggest that the catabolic and immune effects of infection may be a target for clinical intervention in inborn errors of metabolism. *(J Pediatr 2013;163:1705-10)*.

The complete urea cycle occurs in the liver and plays a critical role in the incorporation of excess nitrogen (ie, ammonia) into urea. Portions of the cycle are present throughout the rest of the body and affect arginine production, nitric oxide metabolism, and polyamine production.[1] Urea cycle disorders (UCDs) are caused by loss of function in any of a group of enzymes responsible for the elimination of neurotoxic ammonia. The incidence of these disorders has been estimated at approximately 1 in 30 000 live births.[2]

UCDs may be divided into proximal disorders (deficiencies of N-acetylglutamate synthetase, carbamoyl phosphate synthase, and ornithine transcarbamylase [OTC]), in which ammonia disposal is severely impaired, and distal disorders (deficiencies of argininosuccinate synthetase, argininosuccinate lyase, and arginase), in which ammonia disposal might not be as severely compromised.

The term "precipitant" is used to describe events triggering an acute deterioration in metabolic status. In UCDs, this acute deterioration in metabolic status is characterized by potentially life-threatening episodes of hyperammonemia. Acute hyperammonemia in UCDs may be precipitated by any factor that affects metabolic balance, including dietary indiscretion, and enhanced protein catabolism owing to dietary overrestriction and infection. Intercurrent infection is the most common precipitant of acute hyperammonemia, accounting for 34% of episodes, with respiratory viruses a leading cause.[3,4] Increased nitrogen breakdown secondary to catabolism during these episodes of intercurrent illness is likely a major contributor to acute hyperammonemia.[5] It is a commonly held belief among physicians caring for patients with a UCD that intercurrent infection may result in more severe hyperammonemia episodes with increased morbidity[6]; however, formal studies exploring the various clinical variables of hyperammonemia precipitants are lacking.

IV	Intravenous
LOS	Length of stay
OTC	Ornithine transcarbamylase
RDCRN	Rare Diseases Clinical Research Network
UCD	Urea cycle disorder
UCDC	Urea Cycle Disorders Consortium

From the [1]National Human Genome Research Institute, National Institutes of Health, Bethesda, MD; [2]Pediatrics Epidemiology Center, Department of Pediatrics, University of South Florida, Tampa, FL; and [3]Division of Genetics and Metabolism, Children's National Medical Center, Washington, DC

*A list of Urea Cycle Disorders Consortium members is available at www.jpeds.com (**Appendix**).

Funded by the National Institute of Child Health and Human Development (U54RR19454 and U54HD061221) and the National Institutes of Health (NIH) Office of Rare Diseases Research, and the intramural research program of the NIH (to P.M.). The Urea Cycle Disorders Consortium also is supported by the O'Malley Foundation, the Rotenberg Family Fund, the Dietmar-Hopp Foundation, and the Kettering Fund. The views expressed in written materials or publications do not necessarily reflect the official policies of the Department of Health and Human Services; nor does mention by trade names, commercial practices, or organizations imply endorsement by the US Government. The Urea Cycle Disorders Consortium is a part of the NIH Rare Diseases Clinical Research Network. The authors declare no conflicts of interest.

 http://dx.doi.org/10.1016/j.jpeds.2013.08.029

Given these common perceptions, our goal in the present study was to characterize interim hyperammonemia events and their severity in relation to various precipitating factors. Using data from the Urea Cycle Disorders Consortium (UCDC) longitudinal study,[4] we examined various variables of interim hyperammonemia events, including types of precipitants, plasma ammonia level, hospital admission rate, length of stay (LOS), and hospital-based medical management.

Methods

Participants in the UCDC longitudinal study sponsored by the National Institutes of Health's Rare Diseases Clinical Research Network (RDCRN) for UCDs (U54RR19454 and U54HD61221) were included.[4] The goal of the UCDC is to perform collaborative clinical research on UCDs in the form of an observational longitudinal study. Patients with a UCD were recruited at 16 hospital-based study sites in the US (n = 13), Canada (n = 1), and Europe (n = 2) over a 5-1/2–year period (http://rarediseasesnetwork.epi.usf.edu/ucdc/centers/index.htm). These hospital centers, where study participants underwent periodic clinical evaluation, specialize in the care of patients with inborn errors of metabolism. Sources of referral to the longitudinal study included patient self-referral through the RDCRN, or referral by a medical care provider, prenatal diagnostic center, or the National Urea Cycle Disorders Foundation. Inclusion criteria for hyperammonemia events included all age groups and all UCD diagnoses, including N-acetylglutamate synthase, carbamoyl phosphate synthetase, OTC, argininosuccinate synthetase, argininosuccinate lyase, arginine, and citrin and ornithine transporter defects. Physician-recorded interim event data collected as part of the study included all hospitalizations and urgent clinic visits for symptoms and signs suspicious for acute hyperammonemia. All participating members of the National Institutes of Health–approved RDCRN-UCD study obtained local Institutional Review Board approval.

The present study was a prospective cohort analysis of all physician-reported interim hyperammonemic events recorded after enrollment in the RDCRN-UCD longitudinal study between February 6, 2006, and April 30, 2012. Interim events were defined as plasma ammonia level >100 μmol/L requiring hospitalization, emergency department visit, or urgent clinic visits. Demographic information, history, and clinical and laboratory findings, including the suspected hyperammonemia trigger, were recorded by the treating medical professional and entered into the database.

The association between hyperammonemia morbidity markers and precipitants was examined using the generalized estimating equation assuming a compound symmetry correlation structure, to consider within-subject correlation among those multiple measurements from the same subject. A Poisson distribution was assumed for the count of morbidity markers during the study duration as an outcome, and a normal distribution was assumed for continuously measured markers. Descriptive statistics are presented as number of subjects or events, proportions, and means with SDs.

A P value <.05 was considered to indicate statistical significance. All reported P values are 2-sided, with no adjustment for multiple testing. All statistical analyses were performed using SAS 9.2 (SAS Institute, Cary, North Carolina).

Results

A total of 562 patients with a UCD were enrolled in the longitudinal study database as of April 30, 2012. Among these 562 patients, 128 experienced a total of 413 hyperammonemia events since enrollment (**Table I**); 79% of these patients were aged <18 years. The majority of subjects reporting at least 1 hyperammonemia event had OTC deficiency (52%), followed by citrullinemia (ie, argininosuccinate synthetase deficiency; 20%) and argininosuccinic aciduria (ie, argininosuccinate lysase deficiency; 15%). A slightly higher proportion of the patients with a UCD were female (59%), owing to the large contribution of OTC carrier patients (ie, X-linked disorder). Age at diagnosis, determined by retrospective review, ranged widely, from 6.9 to 2191.5 days (ie, 6.0 years), with most patients identified based on clinical presentation (83%).

Number of Hyperammonemia Events per Individual

Depending on metabolic control, treatment adherence, and exposure to catabolic stressors, patients with a UCD may experience multiple episodes of acute hyperammonemia.[3] Our study population experienced less than 1 event per year on average, attesting to the overall health of the patients enrolled in the longitudinal study (**Table II**). The majority of patients experienced between 1 and 3 (65%) or between 4 and 6 (23%) hyperammonemia events since study inception. Fifteen patients (12%) had experienced ≥6 events since the beginning of the study, and for these individuals, the average number of hyperammonemia events/year was 5 (SD, 4; median, 3; range, 2-12).

Precipitants of Interim Events

Acute hyperammonemia may be precipitated by numerous events, including, but not limited to, infection, dietary or medication changes, and nonadherence with treatment. Medical providers classified the interim events into categories of precipitants (**Table II**). Consistent with previous reports,[3,4] the most common identifiable precipitant was infection (n = 136; 33%), followed by diet (n = 47; 11%). Diet captured nonadherence to the prescribed diet, as well as protein and caloric insufficiency. Systematized Nomenclature of Medicine codes identified upper/lower respiratory tract infections as the most commonly cited type of infection (24%; data not shown). Little overlap was seen between the 2 most common precipitants; only 2% were reportedly triggered by both infection and diet. Almost one-third (31%) of precipitants were classified by medical providers as not belonging to 1 of the other identifiable categories (termed "all other" here), and a small number (3%) were classified as unknown.