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A longitudinal study of urea cycle disorders

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Abstract

The urea cycle disorders consortium (UCDC) is a member of the NIH funded Rare Diseases Clinical Research Network and is performing a longitudinal study of 8 urea cycle disorders (UCD) with initial enrollment beginning in 2006. The consortium consists of 14 sites in the U.S., Canada and Europe. This report summarizes data mining studies of 614 patients with UCD enrolled in the UCDC's longitudinal study protocol. The most common disorder is ornithine transcarbamylase deficiency, accounting for more than half of the participants. We calculated the overall prevalence of urea cycle disorders to be 1/35,000, with 2/3rds presenting initial symptoms after the newborn period. We found the mortality rate to be 24% in neonatal onset cases and 11% in late onset cases. The most common precipitant of clinical hyperammonemic episodes in the post-neonatal period was intercurrent infections. Elevations in both blood ammonia and glutamine appeared to be biomarkers for neurocognitive outcome. In terms of chronic treatment, low protein diet appeared to result in normal weight but decreased linear growth while N-scavenger therapy with phenylbutyrate resulted in low levels of branched chain amino acids. Finally, we found an unexpectedly high risk for hepatic dysfunction in patients with ornithine transcarbamylase deficiency. This natural history study illustrates how a collaborative study of a rare genetic disorder can result in an improved understanding of morbidity and disease outcome.

Keywords

urea cycle; ammonia; hyperammonemia; ornithine transcarbamylase; argininosuccinate lyase; longitudinal study

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1. Introduction

Infants with a complete block in a urea cycle enzyme [other than arginase (ARG)] commonly present in the newborn period with hyperammonemic coma. Despite aggressive treatment with hemodialysis, the five year survival of these newborns was about 50% (pre-2002) [1]. In our initial (1980s) study of these children we found that virtually all survivors had developmental disabilities that correlated with the number, severity and duration of hyperammonemic episodes [2,3]. This poor prognosis prompted some metabolic specialists to recommend that neonatal onset disease not be treated. More recent studies, performed through the NIH funded urea cycle disorders consortium (UCDC), found that the mortality rate from neonatal hyperammonemic coma is less than previously reported and that cognitive outcome, although still concerning, is improving [4]. We also found that patients with partial defects of the urea cycle can manifest hyperammonemia at any age and have a 10% risk of mortality and a significant risk for developmental disabilities [5]. Even asymptomatic ornithine transcarbamylase deficiency (OTCD) heterozygotes, the largest group of UCD patients, have cognitive deficits and are at risk for learning disabilities and attention/executive function deficits [6,7]. These significant findings strongly suggest that former conceptions of outcome in UCD are subject to major revision: survival has improved but this incurs a risk of new and unanticipated co-morbidities that need to be investigated.

Currently, there are three key components to therapy for UCD: (a) pharmacological intervention [8–10], or so-called nitrogen scavenger therapy; (b) nutritional supplementation with the amino acids L-citrulline or L-arginine; and (c) a low-protein diet that balances nitrogen restriction with growth requirements. The only known “cure” for UCD is liver transplantation, which in itself carries a significant morbidity and mortality and does not correct all metabolic abnormalities [11]. As liver transplantation gains acceptance, the long-term outcome of these patients requires study.

Prior to the establishment of the UCDC, morbidity and mortality estimates in UCD were based on a combination of case reports, small retrospective studies from individual metabolic centers and the study of retrospective data from the FDA. The longitudinal study of the UCDC provides a much more accurate picture of the clinical impact of UCD and is beginning to provide a prospective and long-term rather than solely cross-sectional view of the disease.

The UCDC evolved from a core of investigators who in 2000 developed a set of therapeutic guidelines [12]. The need for a long-term dataset on UCD patients was obvious since both the validity of treatment methods and their long-term consequences were largely unknown. The ensuing formation of the UCDC began to answer some of these questions, including the benefit of nitrogen scavenger therapy using phenylbutyrate, the utility of liver transplantation to prevent hyperammonemia, and the need for neuroprotection in acute hyperammonemic crisis [13]. It has also unmasked previously unsuspected issues such as the effects of disruption of nitric oxide, [14,15] the worse than expected neurologic outcome in patients with argininosuccinate lyase deficiency (ASLD), the deleterious effect of high arginine doses on these patients, and a potential increase in hepatic tumor risk [16].

A frequent clinical observation is that infants who recover from neonatal hyperammonemia enjoy a period during which blood ammonia remains normal. This “honeymoon period”, which ranges from weeks to months, is an important component in the natural history of UCD. It gives way to a marked worsening of ammonia homeostasis in later infancy or during the toddler years. An important goal of the longitudinal study is to determine whether these and other widely held clinical impressions can be validated for evidence-based medical practice, since this information could lead to changes in the recommended frequency of follow up, type of monitoring, degree of dietary protein restriction, and approach to drug management. This paper summarizes recent hypothesis-driven data mining projects of the UCDC longitudinal study that attempt to answer some of these questions.

2. Material and Methods

The UCDC was initially funded in Oct 2003; and its longitudinal study protocol was initiated in Feb 2006. There are currently 14 consortium sites, 11 in the U.S., 1 in Canada and 2 in Europe. As of Oct 7, 2013 614 subjects have been enrolled and 561 are currently active in the longitudinal study (Table 1).

Fifty-three subjects are off-study: 11 died, 31 were lost to follow up, 5 were removed at the request of the parent/participant, and 6 were withdrawn from the study by the site PI (usually due to lack of compliance with study follow-up schedule or a failure to agree to re-consenting). This represents a 91% retention rate over 7 years.

We have found that the two most effective sources for the recruitment of patients were from metabolic clinics at UCDC sites and from membership of the National Urea Cycle Disorders Foundation (NUCDF), the patient advocacy organization for this group of disorders. According to study screening records, 74% of participants learned about the longitudinal study through a UCDC physician or coordinator, 11% from NUCDF, 2% from another physician or clinical professional, 2% from the research contact registry, 2% from another study participant, 2% from the internet and 2% from other sources. Hence, nearly three-quarters of participants are patients who receive care in our UCDC recruitment sites. The second most successful recruitment source has been the NUCDF, the patient advocacy organization for UCD. Through its newsletters, annual meetings, and direct contact with its members, the NUCDF has provided information about UCDC studies and encouraged participation.

3. Results

We summarize below a number the data mining results of the longitudinal study grouped into: 1) prevalence (at live birth) and mortality, 2) biomarkers, 3) treatment efficacy, and 4) morbidity including neurodevelopmental outcomes. A number of these studies have been recently published and are referenced.

3.1 BIRTH PREVALENCE AND MORTALITY

3.1.1 Prevalence at Live Birth of Urea Cycle Disorders—Precise determination of the incidence of the UCD is elusive, as is true of most rare diseases. We found a combined

frequency for ASLD and ASSD of 1/117,000 births based upon an analysis of highly sensitive newborn screening data that included over 6 million births in 7 large states¹⁷. We then compared data from the longitudinal study to calculate that patients with these two disorders comprised 30% of urea cycle disorders. A comparison of longitudinal study data with those of the NUCDF and our European sister organization revealed approximately the same value. Using this ratio we estimated that the overall average birth prevalence of urea cycle disorders in the U.S. is 1/35,000 (OTCD 1/63,000, NAGSD/CPSD 1/975,000, and ARGD < 1/1,000,000). Based on an annual birthrate of about 4 million in the U.S., we would predict approximately 114 newborns with a urea cycle disorder to be born each year. From the longitudinal study we find that 26% of participants presented with hyperammonemia in the newborn period (first month of life), 69% presented with symptoms later in life and 5% remained asymptomatic. This would result in about 30 symptomatic newborns being born in the U.S. per year and about 78 new UCD patients presenting after the newborn period each year.

3.1.2. Mortality in UCD—Assessment of case-fatality based on follow-up of enrolled UCDC participants and from record review indicates that mortality from UCD remains high but not as high as earlier reports of 50% in neonatal onset disease. We found a 24% mortality rate in neonatal onset disease. The mortality in late onset disease has not significantly changed from previous reports at 11%. By diagnosis, the risk of mortality (neonatal plus late onset) was greatest in CPS1D (42%), followed by OTCD (11%) ASSD (7%) and ASLD (6%). We cautiously interpret these results as providing support that case-fatality has declined in neonatal onset disease, probably with the advent of neonatal screening for distal UCD, standardization of treatment protocols and improved treatment (including liver transplantation) and earlier recognition of symptomatic UCD.

3.2. BIOMARKERS

3.2.1 Precipitants of acute hyperammonemic episodes in UCD—Our goal was to characterize precipitants of metabolic decompensation as well as the biomarkers that accompany these events. We analyzed longitudinal study data to evaluate several variables, including seasonality, presenting symptoms, putative precipitants, severity of hyperammonemia, hospitalization rates, length of hospital stay, neurologic status, use of dialysis, and biochemical parameters [17]. A total of 128 patients experienced a total of 413 hyperammonemic events since the longitudinal study began. Most patients (65%) experienced between 1–3 episodes of hyperammonemia; while only 23% of patients manifested 4–6 hyperammonemic events. The average was a bit less than 1 hyperammonemic event/year/patient. The most common precipitant was infection (33%) with about 24% of these being respiratory infections based on Systematized Nomenclature of Medicine (SNOMED) codes. Infection was associated with increased hospitalization rates ($P=0.02$), longer hospital stays (+2.0 days, $P=0.003$) and increased use of intravenous ammonia scavengers (to treat the hyperammonemia 45–52%, $P=0.003-0.03$).

3.2.2. Glutamine (Gln) as a biomarker for neurocognitive outcome—Current practice assumes that a plasma Gln level >1000 $\mu\text{mol/L}$ denotes suboptimal ammonia removal, poor metabolic control, and a need for treatment adjustments. Longitudinal study

data were analyzed to determine whether Gln contributes to neurocognitive outcome in patients with UCD. In participants who have had at least two neuropsychological assessments, longitudinal logistic modeling was used to evaluate the odds of worsening neuropsychological test scores in relation to increases in blood Gln and ammonia levels during the same interval, while controlling for initial neurocognitive test scores. We found that the mean of the Gln levels between two assessments predicted the Bayley Motor composite score, the ABAS Social composite score, the Performance IQ (PIQ), and the performance on the California Verbal Learning Test (CVLT) trial 1. Thus, the mean interim Gln levels predict perceptual motor skills including visual reasoning, visual spatial processing, visual motor integration, and attention span which may to some degree be influenced by processing speed [18].

3.3 TREATMENTS

3.3.1. Effect of a prolonged low protein diet on nutritional status and growth—

Descriptive results in the longitudinal study document the complex feeding, nutritional conditions, formulas, supplements and management required to sustain UCD patients. Preliminary trends suggest that protein intake levels for all age groups are higher than recommended allowances, and pediatric growth based on weight is within the expected range, whereas height velocity is lower than expected. Plasma amino acids, ammonia, and biomarkers will refine the assessment of the adequacy of protein intake using generalized estimating equation (GEE) models but these require larger sample size.

3.3.2. Phenylbutyrate (PB) treatment effect on branched-chain amino acids

(BCAA)—In order to assess whether PB treatment decreases plasma levels of BCAA (leucine, isoleucine and valine), we analyzed plasma levels from 595 patients enrolled in the longitudinal study [19]. The use of PB was the independent variable; plasma level of BCAA was the dependent variable. Covariates included age, gender, type of UCD, time of onset of UCD (neonatal vs later onset), protein intake, and plasma levels of pre-albumin and albumin. Data were analyzed using a generalized linear model. Our analysis showed that plasma levels of the BCAA were significantly lower in patients treated with PB, even when accounting for all covariates. Our results indicate that patients with UCD should be routinely monitored for BCAA deficiency and supplemented as required.

3.4. OUTCOME

3.4.1. Neurodevelopmental outcome of children with UCD who undergo liver

transplantation—Sixty-six patients who participated in the longitudinal study received a liver transplant when this analysis was done in January 2013. Of those, 42 patients were transplanted before 2 years of age. We found a trend since 2010 to perform the transplant earlier in the course of disease. The lowest post-transplantation IQ/DQ scores were found in ASLD patients followed by males with OTCD. There were no deaths reported among these patients. Results of neurocognitive testing in the broader group of longitudinal study patients are presented in a companion paper [20].

3.4.2. Acute and chronic hepatocellular injury in OTCD—

As a result of individual observations and case reports we hypothesized that chronic hepatocellular injury as well as

acute liver dysfunction may be under-recognized in OTCD. We reviewed the medical records of patients (n=71) enrolled in the longitudinal study at two centers to assess what proportion with OTCD had evidence of “liver failure” (defined as INR ≥ 2.0), liver dysfunction (INR 1.5–1.99), or hepatocellular injury (AST/ALT ≥ 250 IU/L) [21]. 57% of the 49 patients with symptomatic OTCD had abnormal liver function tests: 29% met the criteria above for liver failure, 20% had liver dysfunction, and 8% had isolated hepatocellular injury. The proportion with liver failure was greatest in those with more severe OTCD, including neonates with markedly elevated ammonia levels ($> 1,000$ $\mu\text{mol/L}$). Some patients with severe liver involvement (INR ≥ 2.0 and aspartate aminotransferase (AST)/alanine aminotransferase (ALT) $> 1,000$ IU/L) had only moderate HA (100 – 400 $\mu\text{mol/L}$). Acute liver failure was the initial presenting symptom of OTCD in at least 3 of 49 symptomatic OTCD patients. We conclude that episodes of hepatocellular injury, liver dysfunction, and acute liver failure occur in a high proportion of individuals with symptomatic OTCD. The more severely affected OTCD patients had a higher likelihood of acute liver failure. This study provides evidence that hepatic injury is extremely common in UCD. We also suggest that the diagnosis of a UCD should be considered in patients with unexplained acute liver failure, dysfunction or hepatocellular injury.

4. Discussion

The UCDC has leveraged federal, foundation and philanthropic funding to form first a national and more recently an international coalition of leading UCD researchers to allow us to make progress in understanding the pathobiology of UCD and in advancing interventions to improve the lives of UCD patients. The UCDC has been highly successful in recruiting and retaining participants in the longitudinal study, which has provided the foundation for new hypotheses and research ideas as well as for recruitment of ancillary studies to exploit these ideas. Ancillary studies have answered some questions but also raised others.

The main theme that emerges is that UCD appear to be more complex than originally thought. Although each of the diagnostic entities in UCD shares a common core pathology associated with hyperammonemia, UCD is anything but homogeneous and is genotypically and phenotypically diverse. It is becoming clear that different mutations within the same diagnostic entity produce different pathogenic profiles and respond to different therapies. On the other hand, it is also clear that other genes and the environment have a major role in the phenotype, since members of the same family affected by the same mutation may have very disparate clinical disease, including no apparent disease at all.

Our studies have found biologically plausible evidence that both glutamine and ammonia have effects on brain function and that each molecule may affect the brain in different ways. There is also evidence that the effects of UCD are more systemic than had been recognized previously, including causing liver disorders and perhaps even liver cancer [16], as well as kidney and vascular pathology via changes in the metabolism of nitric oxide. Lastly, we have seen some preliminary evidence that improved understanding of UCD pathology and improved access to information on UCD management as well as early diagnosis through newborn screening have had a positive impact on mortality and morbidity.

Along with increased pathogenic diversity and complexity comes the requirement for greater participant numbers within specific subgroups, including symptomatic vs. asymptomatic, neonatal vs. later onset, as well as within specific diagnostic entities overall and by severity. There is also a need for longer term follow up because of the potential for progressive organ damage. In addition, new questions that are emerging from the above observations are best addressed prospectively, close to the time of diagnosis, which ongoing enrollment allows.

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Abbreviations

OTCD	ornithine transcarbamylase deficiency
CPS1D	carbamyl phosphate synthetase deficiency
CITRD	Citrullinemia Type II Deficiency
NAGSD	N-acetyl Glutamate Synthase Deficiency
ORNT	(HHH Syndrome) or Mitochondrial Ornithine Transporter Deficiency
ARGD	Arginase Deficiency
ASSD	Argininosuccinate Synthase Deficiency
UCDC	urea cycle disorders consortium
UCD	urea cycle disorders
NUCDF	National Urea Cycle Disorders Foundation
GEE	generalized estimating equation
PB	phenylbutyrate
BCAA	branched-chain amino acids
HA	hyperammonemia

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Appendix

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Highlights

- Mortality rate was 24% in neonatal onset cases and 11% in late onset cases.
- The most common precipitant of clinical hyperammonemic episodes in the post-neonatal period was intercurrent infections.
- Elevations in both blood ammonia and glutamine appeared to be biomarkers for neurocognitive outcome.
- Low protein diets appeared to result in normal weight but decreased linear growth
- N-scavenger therapy with phenylbutyrate resulted in low levels of branched chain amino acids.
- There was an unexpectedly high risk for hepatic dysfunction in patients with ornithine transcarbamylase deficiency.

Table 1

Accrual by Disorder Type as of October 7, 2013

Type of UCD	Neonatal	Late Onset	Frequency of Subtype (Neonatal + Late Onset)	Subtype (Neonatal + Late Onset) Percent of Total Enrolled
OTCD	46	321	367	59.9
ASLD (Argininosuccinate Lyase Deficiency)	46	49	95	15.5
ASSD (Argininosuccinate Synthase Deficiency)	57	30	87	14.2
ARGD (Arginase Deficiency)	1	21	22	3.5
CPS1D	12	5	17	2.8
UCD Highly Likely/Diagnosis Pending	3	9	12	1.8
HHH Syndrome or Mitochondrial Ornithine Transporter (ORNT) Deficiency	1	8	9	1.5
NAGSD (N-acetyl Glutamate Synthase Deficiency)	0	3	3	0.5
CITRD (Citrullinemia Type II Deficiency)	1	1	2	0.3
Total	167	447	614	100