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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 (UCDs) 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 UCDs 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.

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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 UCDs 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 UCDs: (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 UCDs is liver transplantation, which in itself carries a significant morbidity and mortality and does not correct all metabolic

Abbreviations: OTCD, ornithine transcarbamylase deficiency; CPS1D, carbamyl phosphate synthetase deficiency; CITRD, citrullinemia type II deficiency; NAGSD, N-acetyl glutamate synthase deficiency; HHH syndrome, or mitochondrial ornithine transporter (ORNT) deficiency; ARGD, arginase deficiency; ASSD, argininosuccinate synthase deficiency; UCDC, Urea Cycle Disorders Consortium; UCDs, urea cycle disorders; NUCDF, National Urea Cycle Disorders Foundation; GEE, generalized estimating equation; PB, phenylbutyrate; BCAAs, branched-chain amino acids; HA, hyperammonemia.

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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 UCDs 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 UCDs 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 UCDs. 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 UCDs. 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 of 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 UCDs 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 states [17]. 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 UCDs

Assessment of case-fatality based on follow-up of enrolled UCDC participants and from record review indicates that mortality from UCDs 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%),

Table 1
Accrual by disorder type as of October 7, 2013.

Type of UCDs	Neonatal	Late onset	Frequency of subtype (neonatal + late onset)	Subtype (neonatal + late onset) percent of total enrolled
OTCD(ornithine transcarbamylase deficiency)	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 (carbamyl phosphate synthetase deficiency)	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

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