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# Cross-Sectional Multi-Center Study of Patients with Urea Cycle Disorders in the United States

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## Abstract

Inherited urea cycle disorders comprise eight disorders (UCD), each caused by a deficiency of one of the protein that is essential for ureagenesis. We report on a cross sectional investigation to determine clinical and laboratory characteristics of patients with UCD in the United States. The data used for the analysis was collected at the time of enrollment of individuals with inherited UCD into a longitudinal observation study. The study has been conducted by the Urea Cycle Disorders Consortium (UCDC) within the Rare Diseases Clinical Research Network (RDCRN) funded by the National Institutes of Health. One hundred eighty three patients were enrolled into the study. Ornithine transcarbamylase (OTC) deficiency was the most frequent disorder (55%), followed by argininosuccinic aciduria (17%) and citrullinemia (11%). 79% of the participants were white (16% Latinos), and 6% were African American. Intellectual and developmental disabilities were reported in 39% with learning disabilities (35%) and half had abnormal neurological examination. 63% were on a protein restricted diet, 37% were on Na-phenylbutyrate and 5% were on Na-benzoate. 45% of OTC deficient patients were on L-citrulline, while most patients with citrullinemia (58%) and argininosuccinic (79%) were on L-arginine. Plasma levels of branched-chain amino acids were reduced in patients treated with ammonia scavenger drugs. Plasma glutamine levels were higher in proximal UCD disorders and in the neonatal type disease. The RDCRN allows comprehensive analyses of rare inherited UCD, their frequencies and current medical practices.

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**Keywords**

rare diseases network; hyperammonemia; urea cycle disorders consortium; inborn errors of metabolism; clinical research

## INTRODUCTION

With the support of the National Organization for Rare Disorders (NORD) and a coalition of more than 100 Patient Advocacy Groups, Senator Ted Kennedy introduced the Rare Disease Act in August, 2001 [1]. The Bill that was signed into Public Law 107–280 by President George W. Bush in November 2002 intended to enhance research into better diagnosis and treatment for rare disorders, which are estimated to number around 6000 and affect more than 25 million Americans. Public Law 107–280 provided statutory authorization for the NIH Office of Rare Disorders (ORD) and appropriated funds to establish centers of excellence in rare diseases. Requests for applications to establish rare disease research consortia within a Rare Diseases Clinical Research Network (RDCRN) and for a Data and Technology Coordinating Center (DTCC) for the network were released in February 2003. Fifty seven applications for research consortia and 12 applications for a DTCC were received by the NIH. The first 8 RDCRN consortia (including the UCDC which is the source of this report) and the selected DTCC were announced in September 2003. Two additional consortia were funded and became part of the RDCRN within the subsequent two years for a total of 10 rare disease consortia that currently compose the RDCRN. Funding for the network is currently provided from the Office of Rare Diseases and 6 NIH Institutes with funding for the UCDC provided by the National Institute for Child Health and Human Development and the Office of Rare Diseases and for the DTCC by the National Center for Research Resources. The unified goals for each consortium within the network are to: 1) perform collaborative clinical research in rare diseases, including observational longitudinal studies, clinical studies (including phase 1 and 2 trials), and pilot projects; 2) train clinical investigators in rare diseases research; and 3) establish a centralized data repository and data sharing for rare diseases.

This report describes the structure of the UCDC and the methods and preliminary results from its longitudinal study. These early results consist of cross sectional observations and data obtained at the time of enrollment from the first 183 patients with UCD enrolled into the longitudinal study from February 2006 through December 2007.

## METHODS

The UCDC currently consists of 8 research sites located in pediatric academic institutions in the United States from which the results presented herein were collected. Five additional US and international sites are in the process of being added to the UCDC (Figure 1). The UCDC is managed from one of the sites (Children's National Medical Center, Washington DC) and each of the sites has its own principal investigator and research team. Patients who were diagnosed with any one of the 8 known UCD on the basis of the specific diagnostic criteria listed in Table 1 are eligible for the longitudinal study. In addition, patients with hyperammonemia, who are determined as highly likely of having one of the UCD, are also eligible. Patients are recruited from various sources including clinics, patient advocacy groups (National Urea Cycle Disorders Foundation, NUCDF) and a contact registry created by the DTCC (http://rarediseasesnetwork.epi.usf.edu/ucdc/takeaction/registrymenu.htm) where, after electronic informed consent, patients can register confidentially and receive information about studies in any of the RDCRN consortia. Participants can be enrolled into the longitudinal study in any of the 8 sites of the UCDC, with follow up visit taking place either at these sites or, if feasible, at local medical facilities.

During the enrollment visit or around the time of enrollment, the UCDC staff reviews previous medical records and extracts pertinent information. At the visit, the patient and/or guardian(s) are interviewed and the patient undergoes a physical and neurological examination and neuropsychological testing. The information that is collected includes medical and hyperammonemia episode history, review of systems, nutritional history and drug treatment. The patients and/or guardians are asked to provide information on perceived triggers that preceded each recorded hyperammonemia episode as well as the presence of developmental disabilities. Multiple biochemical parameters are measured at the enrollment visit, including plasma amino acids, albumin, total protein, prealbumin, BUN, creatinine, bilirubin, AST, ALT and alkaline phosphatase.

Using the collected data at the time of enrollment, we investigated the characteristics of each type of UCD and associations with various factors. Within each UCD subtype, Fisher's exact test or Chi-square test was employed to examine whether or not the observed frequency of each factor was significantly different, depending on the number of observations. For each biochemical marker, we implemented ANOVA to investigate if there was any difference among UCD subtypes, applying the Tukey-Kramer method to adjust for multiple testing in pair wise comparisons. In addition, two sample t-tests were used to examine the treatment effect. SAS 9.1 (SAS Institute Inc., Cary NC) was used for all analyses.

## RESULTS

In the first 18 months of the study, 183 patients have been enrolled with a total enrollment target of 440 participants. During the same period, 230 individuals self-registered with the DTCC as having one of the UCD (209 reside in the US). All registrants were sent information by the DTCC about the longitudinal study and UCDC sites they can contact to enroll.

Figure 2 illustrates the relative frequency of the various UCD among enrolled participants and those who have registered but did not enroll into the study. OTC deficiency is by far the most frequent among the UCD, accounting for more than half of the participants, followed by AL and AS deficiency which together account for less than a third of the participants. We found that only 27% of those who registered from the US subsequently enrolled in the study. However, this fact did not seem to skew the overall disease frequency results, which were not significantly different between the registered and enrolled groups (Figure 2).

Among enrolled participants with OTC deficiency, 48% are asymptomatic heterozygous females, while 12% are males with neonatal presentation of hyperammonemia. This low proportion of the neonatal type contrasts with a much higher frequency observed in our reference laboratory, which performs diagnostic testing for this disorder. Here the observed frequency of males with neonatal presentation is more than half of all patients from whom samples are referred for molecular testing [2]. Twenty six percent of the OTC deficient patients were hemizygous males who presented clinically after one month of age, while 22% were manifesting heterozygous females who had at least one clinical episode of hyperammonemia.

Table 2 shows, for each disorder, the age at diagnosis, the time elapsed between diagnosis and enrollment into the study and the number of neonatal cases. For most disorders, years elapsed between the median age of diagnosis and the time of enrollment, a pattern that is typical for a cross-sectional study of an existing patient population. Age at enrollment was greatest for OTC deficiency, an X-linked disorder that includes heterozygous females who vary considerably in clinical severity depending upon the pattern of inactivation of the X chromosome. Interestingly, the neonatal presentation comprises the smallest subgroup for OTC deficiency, but the majority of patients in AS and AL deficiency, possibly reflecting better survival of patients with these disorders, even if they present clinically in the neonatal period.

Table 3 shows the ethnic origin of the participants. Of note is the small number of African Americans (6% and 2%) compared to Latinos (16% and 10%), in enrolled and registered patients, respectively. Whether this represents an ascertainment disparity and/or true prevalence of UCD in the population will need to be further investigated.

We studied the disabilities and neurological abnormalities at the time of enrollment, with an emphasis on OTC, AL and AS deficient patients. As seen in Table 4, intellectual disabilities were reported the most (39%), followed by learning disability (35%). AL deficient patients showed significantly higher rates of intellectual disability (p=0.0002 and 0.0154, respectively); they were lower among OTC deficient patients (p=<0.0001 and 0.0097, respectively). Moreover, AL deficient patients had a proportionally higher frequency of seizure disorders (p=0.0082), while patients with OTCD had lower frequency (p=0.0005). Table 5 shows the neurological abnormalities found on neurological examinations that were reported in the medical records. Tone change and reflex abnormalities were reported in 25% of AL deficient and 14% of OTC deficient patients. Abnormalities were significantly higher in AL deficient patients (p=0.0039 and 0.0233, respectively), but lower in those with OTC deficiency (p=0.0274 and 0.0064, respectively).

Long-term treatment of enrolled patients is summarized in Table 6. Sixty three percent of all patients received protein-restricted diets, and 37% (58% of symptomatic patients) have been treated with Na-phenylbutyrate, with a much smaller proportion, 5% (8% of symptomatic patients) treated with Na-benzoate. Forty-five percent of patients with OTC deficiency received L-citrulline, while the majority of patients with citrullinemia and argininosuccinic were given L-arginine (58% and 79% respectively).

Selected comparisons of biochemical markers between UCD subtypes are shown in Table 7. The most significant differences in amino acid levels between UCD subtypes reflect the magnitude of accumulation of the biochemical precursor upstream of the enzymatic block, e.g., citrulline in AS deficiency. Another significant difference is reflected in the level of glutamine, which is higher in patients with proximal urea cycle block (OTC vs. AL deficiency, and OTC vs. AS deficiency).

The amino acid profile stratified by treatment (data not shown) revealed significant correlations. Patients treated with a combination of Na-phenylbutyrate and citrulline showed significant decreases in branched chain amino acids (valine p<0.0001; leucine p<0.0001; isoleucine p<0.0001). On the other hand, alanine and glutamine levels were higher in the phenylbutyrate/citrulline treated group (p=0.0005 and 0.0037, respectively). The amino acid profile, when stratified by neonatal vs. late presentation (data not shown), revealed significant differences in only two amino acids: higher glutamine (p<0.001) and lower citrulline (p<0.0001) levels in the neonatal group.

Several statistically significant differences were noted in these laboratory measures when subjects were stratified based on diagnosis. Of note, subjects with AL deficiency had significantly increased ALT levels compared to both AS deficiency (p<0.02) and OTC deficiency (p<0.001), reflecting the stronger predisposition of patients with AL deficiency to liver disease. In general, no significant differences were noted in the cross-sectional data with respect to nutritional status (albumin, prealbumin, and total protein), kidney function (BUN and creatinine), and liver function (bilirubin, AST, ALT, and alkaline phosphatase) among the different treatment groups (data not shown).

## DISCUSSION

The effective prevention, diagnosis and management of diseases presuppose scientifically rigorous clinical investigation. This goal is difficult if the object of study is a disease of such

rare frequency that few patients are available for study at any one medical center. Statistically valid comparisons in this setting are difficult and often impossible. Multicenter trials are a valid approach toward resolving this problem. The Children's Oncology Group is an excellent example of a longstanding network that investigates best treatment of childhood cancers [3]. This collaborative, multi-institutional approach has markedly improved the outcome of these children and affords a model that is worthy of emulation for other investigations. Fundamental information is lacking for the rare diseases that are the investigative targets of the 10 consortia that compose the RDCRN. Thus, little is known about incidence, prevalence, morbidity, mortality or response to therapy. Hence, the longitudinal studies of the UCDC and the other consortia seek to gather such information in order to provide a rational basis for subsequent clinical trials to improve outcome of conditions that commonly are devastating to patients and families and extremely costly to society in terms of the consumption of health care resources. In addition, the UCDC is also conducting other studies to answer specific questions about UCD. These include research on liver disease in AL deficiency and functional magnetic resonance imaging and spectroscopy to study brain changes in response to ammonia toxicity. These studies and other information about the UCDC are described in the following web site: http://rarediseasesnetwork.epi.usf.edu/ucdc/index.htm.

As demonstrated by these results, support from federal and private philanthropic sources enabled the UCDC to expand from 5 to 8 participant institutions, with imminent plans to bring the total to 14 institutions, 2 of them in foreign sites (Toronto and Zurich). By adding sites from diverse geographic and ethnic regions, we increase the statistical power of the study cohort and lessen the probability of biasing results with an excessively narrow focus.

We found that a relatively small fraction of eligible patients (~ 27%) enrolled in the longitudinal study. This conclusion is supported by the report of the NUCDF that about a third of member families chose to participate. Although this enrollment rate is currently the highest among the RDCRN consortia [4], we are considering strategies to improve enrollment, including changes to the contact registry, engagement with newborn screening programs and enhanced NUCDF advocacy efforts.

Thus far, the distribution of frequency among enrolled and registered UCD patients appears to be consistent with previous estimates [5,6]. OTC deficiency is by far the most frequent among the UCD, followed by AL deficiency (argininosuccinic aciduria) and AS deficiency (citrullinemia). It is expected that the proportional frequency of these latter two disorders will increase in the near future as infants diagnosed by expended newborn screening using tandem mass-spectrometry [7] are enrolled, while several other UCD, especially CPS1 and OTC deficiency cannot be identified by this screening method. Upon final analysis of this study, diagnosis by newborn screening will need to be considered as a confounding factor. Many of patients ascertained by this highly sensitive screening are asymptomatic and may remain so for many years and possibly throughout life. Thus, expanded newborn screening will likely change the natural history of screened UCD as it has done in other screened conditions [8].

A second source of bias appears among patients with OTC (Figure 3). We believe that the proportion of patients with neonatal presentation should be at least equal to those with late onset disease [2]. However, here the proportion of neonatal type patients is much smaller. This can be accounted for by patients who died before being enrolled and/or those who underwent liver transplantation soon after their initial presentation. If this hypothesis is correct, as the study gradually enrolls most patients soon after their first clinical presentation, the proportion of neonatal cases should increase. We are currently performing a retrospective analysis of data from deceased patients with UCD to factor in this bias of selection on study parameter analysis. Since most patients with OTC deficiency are apparently asymptomatic heterozygous females,

it would be interesting if they show subtle deficiencies on neurocognitive testing, as have been suggested previously [9].

Although still preliminary, we observed a marked difference between the number of African American and Latino participants who enrolled. While this could reflect a true difference in disease incidence, it is more likely to be related to disparity in access to medical care and/or targeted advertising of the study and/or mistrust of research due to past abuses [10]. We plan to study this observation further and to increase our efforts to identify and reach under-represented minorities with UCD.

As expected, the ammonia scavenger drug used most frequently in chronic therapy of UCD is oral Na-phenylbutyrate (Bupheny) [11], with Na-benzoate being far less common. L-citrulline (for OTC and CPS deficiency) and L-arginine (for AS and AL deficiency) are used frequently, although not universally. Future analysis will correlate chemical treatment modality with disease severity and other parameters for which information is collected.

Baseline assessment upon enrollment includes self reporting and medical record review with respect to neurodevelopmental parameters, as well as on patient/family perceived triggers of acute episodes of hyperammonemia. A significant proportion of enrolled patients reported developmental disabilities with more than one third reporting intellectual disability, and a similar proportion reported learning disabilities. The effects of recurrent hyperammonemia are known to cause irreversible damage to the brain [12], resulting in the effects reported here. On the other hand, autism and mood disorders have been rarely reported [9], as confirmed by these results. We found a considerably higher rate of developmental disabilities in patients with AL deficiency compared to OTC deficient patients. Although this could merely represent a bias of selection in enrolling a larger proportion of neonatal (severe) cases with AL than with OTC deficiency, it could represent toxic effect of disease metabolites other then ammonia (e.g. argininosuccinic acid) on the brain.

More than half of the enrolled patients had normal neurological examination, while others had a variety of abnormalities such as tone and reflex abnormalities or abnormal involuntary movements. Future analysis will correlate neurocognitive findings with various other factors to try and identify the major risk factors for developing these abnormalities.

The patients and/or their families have identified several triggers that preceded acute hyperammonemic episodes. Not surprisingly, an intercurrent infection was the most frequently cited trigger, followed by a recent change in diet. There were several dozen other triggers listed, however, none of them were implicated in an appreciable frequency.

Most patients expectedly received a protein-restricted diet in order to minimize the production of ammonia from dietary nitrogen. Diet therapy is essential, but in most instances it must be complemented by the use of ammonia scavengers, such as Na-phenylbutyrate (Buphenyl), which has substantially reduced mortality [13]. This agent is especially effective in patients with proximal defects such as deficiencies of OTC and CPS. Patients with distal disorders (AS and AL deficiency) commonly benefit from treatment with both Na-phenylbutyrate and high doses of L-arginine [14]. Surprisingly, arginine therapy was not utilized in almost half of the patients with AS deficiency and about one fourth of those with AL deficiency. This observation may represent the inclusion of milder or asymptomatic cases, such as those diagnosed by newborn screening, or the finding may reflect reduced compliance, non-standard care or both.

These cross-sectional data yielded important insights into the biochemical and pharmacological markers that characterize the UCD. Subjects with a deficiency of either CPS1 or OTC and who presented as newborns had low blood citrulline levels, reflecting the severity of the biochemical block. Almost all patients manifested diminished blood levels of branched-

chain amino acids (BCAA) but following treatment with Na-phenylbutyrate, as previously reported [15]. Other essential amino acids were unaffected. The decrement of blood BCAA may also result from dietary protein restriction, but other indicators of protein insufficiency - including total protein, albumin, and prealbumin – usually were normal. Similarly, citrulline treatment correlated with decreased BCAA, probably reflecting the fact that patients with a deficiency of OTC typically receive both Na-phenylbutyrate and citrulline. Not surprisingly, blood levels of major nitrogen carriers, such as glutamine and alanine, were significantly decreased in individuals who received these agents. As observed previously [16], patients with proximal urea cycle disorders (CPS1 and OTC deficiency) display higher plasma levels of glutamine than those with distal disorders (AS, AL and ARG deficiency), probably reflecting the sequestration of waste nitrogen in citrulline, argininosiccinate or arginine, respectively.

Multicenter collaborative clinical research of a group of inborn errors of metabolism, such as UCD, allows for the first time insights into the natural history and clinical practice of these disorders. In spite of many challenges to enroll patients and potential bias of selection, the information that has been already garnered and future prospective data, are likely to markedly improve our understanding of these devastating disorders and offer better approaches to their treatments. The main benefits from this effort are yet to be realized. This will likely occur only after years of prospective study of enrolled patients, with the full participation of many clinical centers.

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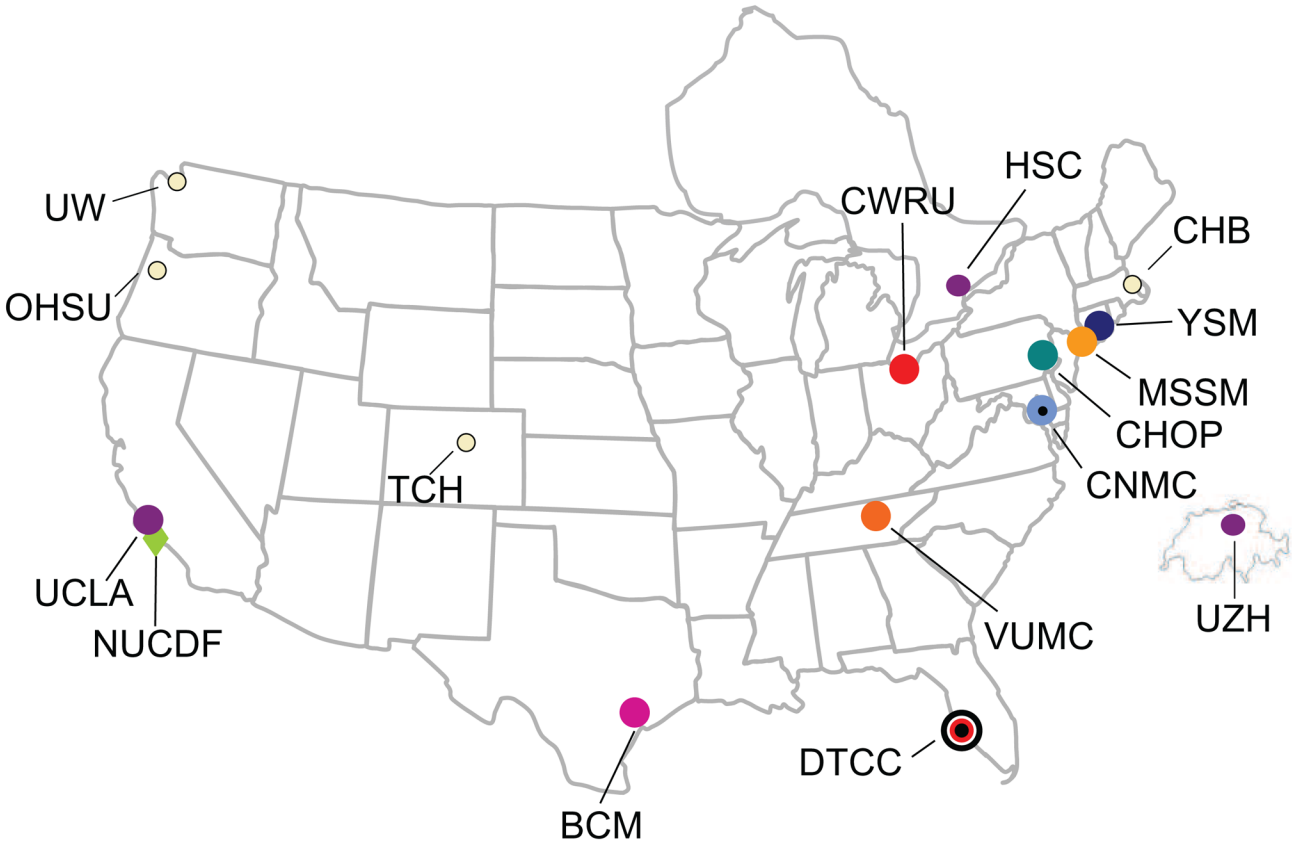


**Figure 1.**

The Urea Cycle Disorders Consortium currently consists of 8 sites. Children's National Medical Center (CNMC) The George Washington University, Washington, DC; Children's Hospital of Philadelphia (CHOP) University of Pennsylvania, Philadelphia, PA; Mount Sinai School of Medicine (MSSM), New York, NY; Yale University School of Medicine (YSM), New Haven CT; Vanderbilt University School of Medicine (VUSM), Nashville, TN; Baylor College of Medicine (BCM), Houston, TX; Case Western Reserve University (CWRU), Cleveland OH; University of California Los Angeles, Los Angeles, CA. Additional sites are being added at the time of this report in: Children's Hospital Boston (BCH); Harvard University, Boston, MA; The Children's Hospital (TCH), University of Colorado, Denver, CO; Oregon Health and Sciences University (OHSU), Portland, OR; University of Washington (UW), Seattle WA; Hospital for Sick Children (HSC), Toronto, Canada; University of Zürich (UZH), Zürich Switzerland. The Data Technology and Coordinating Center (DTCC) is located at the University of South Florida, Tampa, FL, and the National Urea Cycle Disorders Foundation (NUCDF) has its headquarters in La Canada, CA.

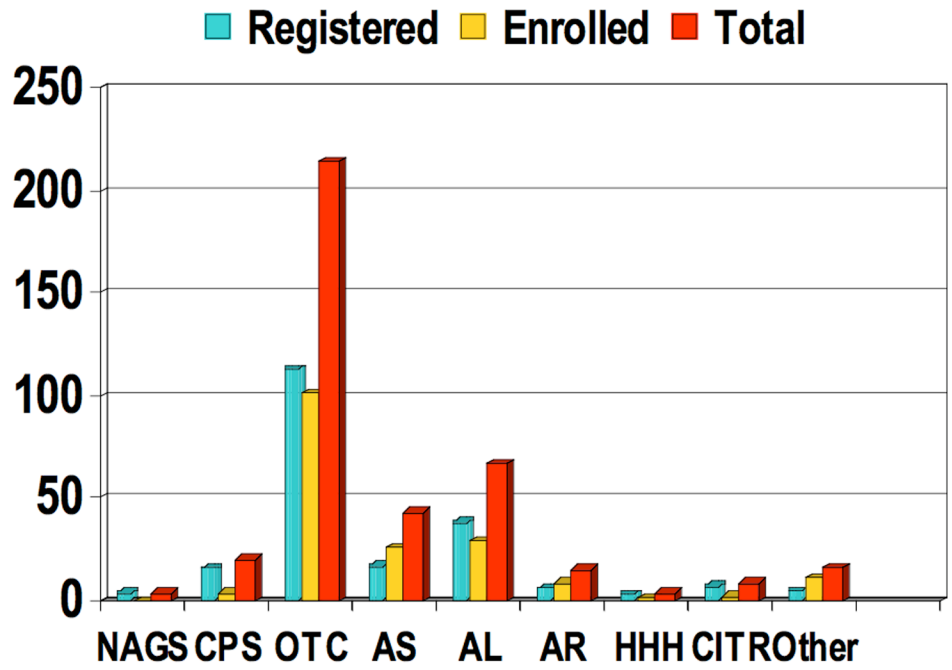


**Figure 2.**
Frequency of the various urea cycle disorders among patients that have enrolled, registered but not enrolled, and the combination of the two groups. The category designated "Other" includes those patients with a highly likely diagnosis of a urea cycle disorder but for whom the specific diagnosis is still pending.

**Table 1**

Diagnostic (inclusion) criteria for patients enrolled in the longitudinal study of urea cycle disorders

| Disorder | Diagnostic (Inclusion) Criteria |
|---|---|
| NAGS Deficiency | ▪ identification of pathogenic mutation and/or<br>▪ decreased (<20% of control) NAGS enzyme activity in liver |
| CPS1 Deficiency | ▪ decreased (<20% of control) CPS I enzyme activity in liver and/or<br>▪ identification of pathogenic mutation |
| OTC Deficiency | ▪ identification of pathogenic mutation and/or<br>▪ pedigree analysis and/or<br>▪ <20% of control OTC activity in liver and/or<br>▪ elevated urinary orotate (>20 umol/mmol creatinine) after allopurinol challenge test |
| AS Deficiency (Citrullinemia) | ▪ ≥10 fold elevation of citrulline in plasma and/or<br>▪ decreased AS enzyme activity in cultured skin fibroblasts or other appropriate tissue and/or<br>▪ identification of pathogenic mutation |
| AL Deficiency (Argininosuccinic Aciduria, ASA) | ▪ presence of argininosuccinic acid in blood or urine and/or<br>▪ decreased AL enzyme activity in cultured skin fibroblasts or other appropriate tissue and/or<br>▪ identification of pathogenic mutation |
| ARG Deficiency (Argininemia) | ▪ ≥5 fold elevated arginine in blood and/or<br>▪ decreased arginase enzyme level in red blood cells or other appropriate tissue and/or<br>▪ identification of pathogenic mutation |
| HHH Syndrome or ORNT Deficiency | ▪ ≥5 fold elevated plasma ornithine and of homocitrulline in urine and/or<br>▪ identification of pathogenic mutation |
| CITR Deficiency (Citrullinemia Type II) | ▪ elevated citrulline in blood and/or identification of pathogenic mutation |
| UCD Highly Likely/ Diagnosis Pending | ▪ Laboratory values highly suggestive of a UCD with symptomatic hyperammonemic episodes but without a current specific diagnosis |

**Table 2**

Proportion of neonatal cases, age at enrollment and time from diagnosis

| Disorder | N (%)[1] | Neonatal N (%)[2] | Age at enrollment in years median (range) | Difference in years between ages at enrollment and at diagnosis median (range) |
|---|---|---|---|---|
| AL | 29 (16) | 18 (62)* | 8 (0–26) | 7 (0–26) |
| ARG | 9 (5) | 1 (11) | 12 (1–45) | 7 (1–33) |
| AS | 26 (14) | 19 (73)* | 6.5 (0–28) | 2.5 (0–28) |
| CITR | 2 (1) | 0 (0) | 3 (3–3) | 2 (2–2) |
| CPSI | 4 (2) | 3 (75) | 15.5 (7–23) | 11 (7–19) |
| HHH | 1 (1) | 0 (0) | 3 | 0 |
| OTC | 101 (55) | 8 (8)* | 20 (1–71) | 5 (0–37) |
| UCD likely | 11 (6) | 1 (9) | 12 (1–84) | 5 (0–24) |
| Total | 183 | 50 (27) | | |

*P<0.05 comparing proportion of neonatal cases between patients with each UCD and all other patients

[1]Proportion in all 183 enrolled patients.

[2]Proportion within each UCD subtype

**Table 3**

Race and ethnicity distribution among UCD patients

| Ethnic Group | Registered (209) | Enrolled (183) |
|---|---|---|
| Alaskan/Native | 0 | 0 |
| Asian | 3 | 12 |
| Black | 4 | 9 |
| Hawaiian | 1 | 0 |
| White | 189 | 145 |
| Unknown/not reported/more than one race | 12 | 17 |
| Latino | 21 | 30 |

**Table 4**

Self-reported developmental disabilities and psychiatric disorders in enrolled patients: N (%)

| Disorder | adhd | asd | cd | cp | idd | ld | md | pd | sd | vhi |
|---|---|---|---|---|---|---|---|---|---|---|
| Neonatal | 8 (17) | 0 | 9 (28)* | 3 (7) | 28 (61)* | 19 (41) | 0 | 0 | 12 (26)* | 6 (13) |
| AL | 8 (30)* | 0 | 2 (14) | 1 (4) | 19 (70)* | 14 (56)* | 0 | 4 (15) | 8 (32)* | 3 (12) |
| AS | 5 (20) | 0 | 4 (21) | 1 (4) | 14 (56) | 9 (36) | 0 | 0 | 4 (16) | 3 (12) |
| OTC | 11 (12) | 1(1) | 7 (9) | 1 (1) | 22 (23)* | 25 (26)* | 3 (12) | 10 (11) | 6 (6)* | 13 (14) |
| Others | 2 (13) | 0 | 2 (18) | 2 (13) | 9 (60) | 8 (53) | 0 | 0 | 6 (40)* | 3 (20) |
| UCD likely | 2 (20) | 0 | 1 (11) | 0 | 3 (30) | 3 (30) | 0 | 0 | 1 (10) | 0 |
| Total | 28 (17) | 1 (0.6) | 16 (13) | 5 (3) | 67 (39) | 59 (35) | 3 (7) | 14 (8) | 25 (15) | 22 (13) |

adhd: attention deficit hyperactivity disorder; asd: autism spectrum disorder; cd: communication disorder; cp: cerebral palsy; idd: intellectual disability; ld: learning disability; md: mood disorder; pd: other psychiatric disorder; sd: seizure disorder; vhi: visual or hearing impairment.

*P<0.05 comparing frequency of self-reported disability between patients with each disorder and all other patients.

**Table 5**

Abnormal findings reported from neurological evaluation: N (%)

| Disorder | abm | asy | cere | cont | namb | ref | tc | vish |
|---|---|---|---|---|---|---|---|---|
| Neonatal | 5 (14) | 4 (11) | 4 (11) | 0 | 1 (3) | 6 (16) | 14 (38)* | 3 (8) |
| AL | 4 (20) | 2 (10) | 3 (15) | 0 | 0 | 6 (30)* | 10 (50)* | 1 (5) |
| AS | 4 (21) | 2 (11) | 3 (16) | 0 | 1 (5) | 3 (16) | 3 (16) | 3 (16) |
| OTC | 4 (6)* | 7 (11) | 5 (8) | 0 | 0 | 4 (6)* | 11 (17)* | 3 (5) |
| Others | 2 (20) | 0 | 1 (10) | 1 (10) | 1 (10) | 3 (30) | 4 (40) | 1 (10) |
| UCD likely | 2 (29) | 0 | 0 | 0 | 0 | 1 (14) | 2 (29) | 0 |
| Total | 16 (13) | 11 (9) | 12 (10) | 1 (0.8) | 2 (2) | 17 (14) | 30 (25) | 8 (7) |

abm: abnormal movement; asy: asymmetry; cont: contractures; cere: cerebellar findings; namb: not ambulatory; tc: tone changes; ref: reflex abnormalities; vish: visual/hearing deficits.

*P<0.05 comparing frequency of neurological abnormality between patients with each disorder and all other patients.

**Table 6**

Chronic treatment of UCD patients: N (%)

| Disorder | Phenylbutyrate | Arginine | Benzoate | Citrulline | Protein restriction |
|---|---|---|---|---|---|
| AL | 6 (21) | 23 (79) | 2 (7) | 0 (0) | 22 (76) |
| AS | 13 (50) | 15 (58) | 1 (4) | 0 (0) | 17 (65) |
| OTC | 36 (37) | 2 (2) | 1 (1) | 44 (45) | 58 (57) |
| Others | 4 (25) | 0 (0) | 3 (19) | 3 (19) | 10 (63) |
| UCD likely | 7 (64) | 1 (9) | 2 (18) | 9 (82) | 8 (73) |
| Total | 66 (37) | 41 (23) | 9 (5) | 56 (31) | 115 (63) |

**Table 7**

Biochemical markers in UCD subtypes: Mean(SD)

| Marker | AL | AS | OTC | Others | p | significant difference |
|---|---|---|---|---|---|---|
| **Amino acid** | N=25 | N=24 | N=92 | N=24 | | in pairwise comparison |
| Alanine | 345(104) | 423(229) | 478(206) | 357(174) | 0.003 | OTC vs (AL, Others) |
| Arginine | 95(84) | 71(38) | 64(33) | 145(120) | <0.0001 | Others vs (AL, AS, OTC) |
| Citrulline | 184(90) | 1685(1325) | 29(25) | 99(336) | <0.0001 | AS vs (AL, OTC, Others) |
| Glutamine | 607(203) | 579(265) | 859(381) | 710(277) | <0.0001 | OTC vs (AL, AS) |
| Isoleucine | 43(18) | 41(27) | 48(24) | 45(32) | 0.5471 | |
| Leucine | 81(37) | 75(45) | 89(41) | 75(50) | 0.3256 | |
| Valine | 146(42) | 145(71) | 166(69) | 132(72) | 0.1154 | |
| **Protein** | N=26 | N=25 | N=95 | N=27 | | |
| Total Protein | 6.6(1.4) | 6.9(0.6) | 7.3(0.6) | 7.0(0.8) | 0.0002 | AL vs OTC |
| Albumin | 4.1(0.5) | 4.1(0.4) | 4.1(0.7) | 3.9(0.7) | 0.3935 | |
| Prealbumin | 23.6(8.4) | 24.4(7.2) | 22.7(6.2) | 19.4(6.2) | 0.073 | |
| **Kidney** | N=26 | N=23 | N=95 | N=27 | | |
| BUN | 10.1(4.9) | 6.7(3.9) | 10.0(5.8) | 7.1(5.2) | 0.0079 | AS vs OTC |
| Creatinine | 0.4(0.2) | 0.4(0.2) | 0.6(0.2) | 0.5(0.2) | 0.0001 | OTC vs (AL, AS) |
| **Liver** | N=26 | N=24 | N=97 | N=26 | | |
| ALT | 92.0(143.4) | 38.5(22.5) | 37.2(35.8) | 59.0(56.4) | 0.002 | AL vs (AS, OTC) |
| AST | 61.7(73.5) | 38.5(11.5) | 31.7(24.4) | 52.0(39.7) | 0.0014 | AL vs OTC |
| Alk Phos | 212(110) | 220(107) | 161(115) | 211(99) | 0.0235 | |