Greetings from the UCDC Leadership

Dear Urea Cycle Disorders Consortium research participants,

First, I would like to thank you for your participation in urea cycle disorders (UCD) research. With your help we have been able to conduct observational studies and clinical trials that have added to our knowledge of UCDs and how to treat them. The research has led to changes in treatment guidelines and has helped us secure a second cycle of NIH funding.

We would like to share with you some of the accomplishments that we have made together and findings from some of our studies. Many of you are enrolled in the Longitudinal Study of Urea Cycle Disorders; we have started to analyze this data, which has led to nine publications to date, six of which are summarized in this newsletter. The full articles are available on our website (www.RareDiseasesNetwork.org/ucdc). If you have any questions about the summaries or the articles, don’t hesitate to talk to the physician or coordinators at your clinical site. We are happy to discuss the findings with you and answer any questions you might have.

We are currently working on several more projects using the Longitudinal Study data, including studying cognitive outcomes in proximal vs. distal urea cycle disorders, liver failure, and nutrition analysis. We hope to publish our findings from these projects in the near future and will continue to share the results with you.

In addition to the Longitudinal Study, the UCDC is working on several other UCD studies. Dr. Andrea Gropman at Children's National Medical Center has concluded one neuroimaging study and published several papers as a result. She is currently recruiting participants with OTC for another study that uses neuroimaging study to look at biomarkers. These studies are described in more detail in this newsletter and one of Dr. Gropman’s pivotal papers is summarized on page 7.

Dr. Brendan Lee and his team at Baylor College of Medicine have recently completed a study of participants with ASA looking at use of high and low doses of arginine with sodium phenylbutyrate. A summary of his findings will be published shortly and will be included in our next newsletter.

We are enrolling subjects in our Carbaglu in the Treatment of Hyperammonemia Study, in the Carbaglu Surveillance Study that we are doing in conjunction with Orphan Europe, and in our Oxidative Stress Study. We will be opening a Nitric Oxide Study in the Spring.

We are very excited about what we have learned from these important studies so far and look forward to continuing our work with you to keep learning about UCD. Our goal is to improve the outcome of all individuals with UCDs and to spread knowledge about these disorders so physicians can treat them more rapidly and effectively. We thank you for your help in making this possible.

Mark Batshaw, MD
Director, Urea Cycle Disorders Consortium
On behalf of all of the National Urea Cycle Disorders Foundation and our UCD patients and families around the world, I would like to thank you for your contribution to moving UCD research forward! Your participation in the Longitudinal Study and other important UCD studies has increased the understanding of UCDs and made it possible for researchers to delve deeper into the many questions we have had for so long about UCDs and the effects on our UCD children and adults. By standing together as a UCD community focused on research progress, you have helped to catalyze the development of new interventions and therapies to improve the lives of patients with UCD.

We are so pleased to be able to report the findings of the UCDC studies to you -- accomplishments you helped make possible in a relatively short time. We need to learn much, much more about the mysteries of UCDs. The new research projects will help unlock these mysteries, and your continued participation will be the key.

We look forward to keeping you posted about the progress of the studies. Thank you again for your commitment to accelerating this critical research. If you have any questions or would like to privately discuss the studies or your participation, please don’t hesitate to contact me at NUCDF.

Best regards,

Cynthia Le Mons

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### The Longitudinal Study of Urea Cycle Disorders

The Longitudinal Study of Urea Cycle Disorders is an observational study of the natural history of UCD, which aims to find out how well current treatments are working, find better ways to treat UCD, and prevent and predict symptoms that occur with UCD.

The Longitudinal Study has been enrolling participants since February 2006 and has 521 participants enrolled as of January 1, 2012. The Longitudinal Study has led to several publications to date. This section contains a summary of selected published articles resulting from the Longitudinal Study. The full articles are available on our website: [www.RareDiseasesNetwork.org/ucd](http://www.RareDiseasesNetwork.org/ucd).

### Establishing a Consortium for the Study of Rare Diseases: The Urea Cycle Disorders Consortium


The Urea Cycle Disorders Consortium (UCDC) was created as part of a larger network established by the National Institutes of Health to study rare diseases. This paper reviews the UCDC’s accomplishments over the first six years, including how the Consortium was developed and organized, clinical research studies initiated, and the importance of creating partnerships with patient advocacy groups, philanthropic foundations and biotech and pharmaceutical companies.

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


This 2008 report investigates clinical and laboratory characteristics of patients with urea cycle disorders (UCDs) in the United States using data collected from the Longitudinal Study of Urea Cycle Disorders. Rather than looking at data collected over time, this analysis was limited to data collected at

(Continued on page 3)
Intellectual, Adaptive, and Behavioral Functioning in Children with Urea Cycle Disorders


Urea cycle disorders can lead to an accumulation of ammonia in the blood and brain and result in neurodevelopmental disabilities. This analysis of data from the Longitudinal Study of Urea Cycle Disorders was to describe the intellectual, adaptive, and emotional/behavioral functioning of children with Urea Cycle Disorders (UCDs). Intellectual functioning refers to a person’s ability to learn, think, solve problems, and make sense of the world. Adaptive behavior includes the age-appropriate behaviors necessary for people to live independently and to function safely and appropriately in daily life. Adaptive behaviors include real life skills such as grooming, dressing, safety, safe food handling, school rules, ability to work, money management, cleaning, making friends, social skills, and personal responsibility expected based on age. Emotional/behavioral functioning measures assess one’s ability to learn, build and maintain interpersonal relationships, behavior, feelings, mood, and fears.

These domains were measured through testing and parent questionnaires in 92 children with UCDs (33 neonatal onset, 59 late onset). Results show that children who present with UCD later in childhood have better outcomes than those who present with neonatal onset UCD (symptoms in the first month of life). Approximately half of the children with neonatal onset UCD performed in the range of intellectual disability (ID), including about 30% who were severely impaired. In comparison, only a quarter of the late onset group were in the range of ID. There is also evidence that those with UCD have difficulties with some emotional/behavioral and executive function skills (difficulties with behavior regulation, organization, and goal directed behaviors). In conclusion, children with UCDs present with a wide spectrum of intellectual and behavioral outcomes. Children with neonatal onset UCDs have a much higher likelihood of having an intellectual disability, which becomes more evident with increasing age. However, even children with late onset UCDs demonstrate evidence of neurocognitive (intellectual) and behavioral impairment, particularly in aspects of attention and executive functioning (intellectual processes).
Arginase I Deficiency: Severe Infantile Presentation with Hyperammonemia: More Common than Reported?


Enzyme defects of the urea cycle typically present with significant hyperammonemia (high ammonia levels) in the first few months of life. However, arginase I (ARG1) deficiency has classically been the exception. ARG1 deficiency usually presents later in life with spasticity, seizures, failure to thrive, and developmental regression. Neonatal and early presentation as an infant with severe hyperammonemia remains rare and only six such cases have been described. We report a severely affected infant with ARG1 deficiency who presented at six weeks of age with lethargy, poor feeding and severe encephalopathy (abnormal brain function) caused by high ammonia levels. This paper reviews the clinical and biochemical features of this infant and six other previously reported cases of neonatal or early presentation ARG1 deficiency. In addition, this paper presents the clinical spectrum of seven previously unpublished patients with later onset ARG1 deficiency, who also experienced recurrent hyperammonemia. Several biochemical abnormalities have been thought to play a role in the neurological changes in ARG1 deficiency including high arginine levels, elevated guanidino compounds and elevated glutamine levels, as well as the high ammonia levels. Our case demonstrated many of these. The cases reviewed suggest a correlation between genotype (inherited information) and phenotype (actual observed properties) and provide support for the addition of arginine as a primary target in newborn screening programs.

Vaccines Are Not Associated With Metabolic Events in Children With Urea Cycle Disorders


Despite the success of childhood immunizations in prevention of infectious diseases, questions remain about the safety of vaccines in medically fragile children with inborn errors of metabolism such as urea cycle disorders (UCDs). Patients with UCDs are subject to hyperammonemic episodes (HAEs) (episodes of elevated ammonia levels) after infection, fever, or other stressors. We sought to assess the risk of HAEs that required urgent care or hospitalization after routine vaccinations in pediatric patients with underlying UCDs. This was an investigation of vaccine safety in children with UCDs from data collected from the Longitudinal Study of Urea Cycle Disorders. Post-vaccination exposure periods were defined as 7 or 21 days after any immunization. The study included 169 children younger than 18 years. Of these children, 74 had records of at least 1 HAÉ and at least 1 vaccination. With adjustment for age, there was no increase in relative incidence of HAEs in either the 7-day or 21-day exposure period after vaccination compared with HAEs outside of the vaccination periods. No vaccine type was associated with significantly more HAÉs. We found no statistically significant association between childhood immunizations and HAÉs in children with UCDs. The results support the safety of immunization in this medically vulnerable population.
Hepatocellular Carcinoma in a Research Subject with Ornithine Transcarbamylase Deficiency

Wilson JA, Shchelochkov OA, Gallagher RC, Batshaw ML. Molecular Genetics and Metabolism In Press.

A 66 year old woman with symptomatic ornithine transcarbamylase deficiency (OTCD) presented with hepatocellular carcinoma (HCC) (liver cancer). Fourteen years before being diagnosed with HCC she participated in a phase I gene therapy study which used an adenoviral vector to deliver a normal OTC gene to hepatocytes. The vector used is not thought to cause cancer. A recent review of data collected by the Longitudinal Study of Urea Cycle Disorders found three additional patients being treated for HCC which is higher than would be anticipated in this population. This suggests that those with urea cycle disorders (UCDs) may be at increased risk of developing liver cancer as has been observed in certain other inborn errors of metabolism. We will be studying this further to determine if there is, in fact, an increased risk of liver cancer in urea cycle disorders that could be related to chronic liver inflammation. If this is found to be the case, we might recommend annual abdominal ultrasounds for early detection of liver cancer as is recommended for other disorders that have an increased risk of liver cancer. At this point it is too soon to make these recommendations or establish guidelines, as additional studies are needed.

Other UCDC Studies

In addition to the Longitudinal Study of Urea Cycle Disorders, we have several other studies that have been completed or are currently ongoing:

**Complete**

A Randomized, Double-Blind, Crossover Study of Sodium Phenylbutyrate (Buphenyl™) and Low-Dose Arginine (100 mg/kg/day) Compared to High-Dose Arginine (500mg/kg/day) Alone on Liver Function, Ureagenesis and Subsequent Nitric Oxide Production in Patients with Argininosuccinic Aciduria (ASA): Patients with ASA have long-term complications including liver dysfunction and hypertension. It is thought that these complications may be due, in part, to accumulation of argininosuccinic acid upstream of the metabolic block or deficiency of arginine downstream of the block. In order to test this hypothesis, we conducted this trial comparing high-dose arginine alone with low-dose arginine with sodium phenylbutyrate in 12 patients with ASA. Results will be reported in our next issue of the UCDC Update Newsletter.

Assessing Neural Mechanisms of Injury in Inborn Errors of Urea Metabolism Using Structural MRI, Functional MRI, and Magnetic Resonance Spectroscopy: This neuroimaging study using structural magnetic resonance imaging, functional magnetic resonance imaging, and magnetic resonance spectroscopy is complete. Another project has grown out of this study and uses a neuroimaging scheme to evaluate a series of brain biomarkers and their association with neural injury and recovery in a group of urea cycle disorders (see the neuroimaging study described below). Several publications have been published, one of which is summarized on page 7. Other findings will be focused on in our next UCDC Update Newsletter.

**Open for Enrollment**

N-carbamylglutamate in the Treatment of Hyperammonemia: N-carbamylglutamate is a chemical compound with a similar structure to N-acetylglutamate, which is essential to the first step of the urea cycle. In this study, we investigate the effect of N-carbamylglutamate (NCG, Carbaglu®) on ureagenesis (metabolism of amino acids to urea) in patients with any of four inborn errors of metabolism that cause hyperammonemia including: carbamyl phosphate synthetase I (CPSI) deficiency, ornithine transcarbamylase (OTC) deficiency, propionic acidemia (PA) and methylmalonic acidemia (MMA). One of the articles resulting from this study is summarized on page 6.

The Carbaglu Surveillance Protocol: The purpose of this study is to conduct post-marketing surveillance of carglumic acid (Carbaglu) to obtain long-term clinical safety information. Carglumic acid was approved by the United States Food and Drug Administration (FDA) for treatment of hyperammonemia due to N-acetylglutamate synthase (NAGS) deficiency. Much of the FDA-
required data is already collected through the Longitudinal Study of Urea Cycle Disorders. This study will collect additional data on adverse events, adverse reactions, pregnancy, and fetal outcomes in patients with NAGS deficiency who are taking Carbaglu.

Investigation of Brain Nitrogen Metabolism in Partial Ornithine Transcarbamylase Deficiency (OTCD) Using 1H MRS, DTI, and fMRI: This neuroimaging study tests the hypothesis that stable patients with UCD have specific brain biomarkers that can be measured by sophisticated neuroimaging studies (diffusion tensor imaging (DTI), functional magnetic resonance imaging (fMRI) and magnetic resonance spectroscopy (MRS)) and that the levels of these biomarkers correlate with the clinical severity of the disorder and outcome. Biomarkers are biological indicators of a process, event, or condition in the body. For example, Dr. Gropman’s studies have found that OTC deficiency participants experience high levels of the amino acid glutamine, even if they don’t experience symptoms of hyperammonemia. One of the articles resulting from this study is summarized in the next section.

Coming Soon
Pilot Project - Oxidative Stress, Inflammation and the Acute Metabolic Decompensation in Urea Cycle Disorders: Oxidative stress markers measure physiological stress on the body. Inflammatory cytokines are a kind of protein secreted by cells during inflammation. The aims of this study are to test the hypotheses that: 1) measuring oxidative stress markers and inflammatory cytokine levels show if UCDs are under metabolic control and 2) oxidative stress markers and inflammatory cytokines will change as ammonia levels change. This information would predict if a hyperammonemic episode is likely to occur soon and permit prevention or early treatment.

Pilot Project - Nitric Oxide Flux and Ureagenesis in ASS deficiency: In addition to their function in the urea cycle, many tissues express two urea cycle enzymes, for example argininosuccinic acid lyase or ASL (the deficient enzyme in argininosuccinic aciduria) and argininosuccinic synthetase or ASS, the deficient enzyme in citrullinemia) for generation of arginine. This role played by ASL in generating arginine and thus nitric oxide has been implicated in causing many of the long term complications, such as, hypertension (high blood pressure) and liver dysfunction. If the decreased arginine recycling were to be the reason for the complex clinical findings in ASL deficiency, it would be reasonable to expect that ASS deficiency also leads to comparable clinical problems. However, this is not the case and hence raises the questions: 1) Are ASS patients deficient in nitric oxide production? and 2) Is there a difference in the relative importance of ASL vs ASS in generation of nitric oxide? This pilot study aims to answer these questions.

N-carbamylglutamate in the Treatment of Hyperammonemia
Effects of a Single Dose of N-carbamylglutamate on the Rate of Ureagenesis

We studied the effect of a single dose of N-carbamylglutamate (NCG, Carbaglu®) on increasing urea cycle activity in healthy young adults. In 5 of 6 individuals who were studied the administration of NCG increased urea production. No untoward side effects were observed. The data indicate that treatment with NCG stimulates urea cycle enzyme activity and could be useful in clinical settings of acute hyperammonemia of various causes. NCG has shown significant improvement in participants with N-acetylglutamate synthetase (NAGS) deficiency. This study is being continued to determine the effect of NCG on urea cycle activity in patients with carbamyl phosphate synthetase 1 (CPSI) deficiency, ornithine transcarbamylase (OTC) deficiency, propionic acidemia (PA) and methylmalonic acidemia (MMA).
Investigation of Brain Nitrogen Metabolism in Partial Ornithine Transcarbamylase Deficiency (OTCD) Using 1H MRS, DTI, and fMRI


Ornithine transcarbamylase deficiency (OTCD) has been shown to result in white matter brain injury and impairments in working memory and executive cognition. Executive cognition is the term for cognitive processes such as planning, attention, problem solving, verbal reasoning, inhibition, mental flexibility, multi-tasking, initiation and monitoring of actions. The objective of this study was to test for differences in blood oxygenation level-dependent (BOLD) signal activation between participants with OTCD and healthy controls during a working memory task. BOLD is a noninvasive imaging technique using functional magnetic resonance imaging (fMRI) to look at the contrast between oxygenated and deoxygenated hemoglobin. Hemoglobin is the iron-containing part of red blood cells that transports oxygen throughout the body. BOLD can be used to look at blood flow in the brain and shows metabolic activity in the brain. A working memory task was performed while the participant was scanned using the 3T fMRI scanner. In participants with OTCD, we found increased BOLD signal in the right dorsolateral prefrontal cortex and anterior cingulated cortex relative to healthy age-matched controls. In summary, OTCD participants showed increased neuron (nerve cell) activation when performing the same task as healthy volunteers. This points to less than optimal activation of the working memory network in the OTCD participants, most likely due to damage caused by hyperammonemic events. In other words, OTCD participants’ brains are working harder to accomplish the same task as healthy controls. Future studies using higher cognitive load are needed to learn more about these effects.

Take Action

Many of you are already registered with the RDCRN Contact Registry. If you haven’t registered, consider doing so, so that you can receive the most current information on:

- Open recruitment for clinical studies of your disorder
- Opening of new UCDC clinical sites
- Awareness and advocacy group activities
- Information about future opportunities to participate in UCD research

Contact Registry Link: http://rarediseasenames.rarediseasesnetwork.epi.usf.edu/ucdc/takeaction/registrymen.htm

*The Contact Registry is a way for you to provide your contact information so that the UCDC can contact you to keep you informed about UCD research. It does not facilitate contact between individuals with UCD.

Your Feedback Is Important To Us

Please let us know what you think about our first issue of UCDC Update. Please go to https://www.surveymonkey.com/s/UCDCUpdateFeedback to complete the newsletter survey on-line or fill out this short-version and mail it to us at:

Jennifer Seminara, Children’s National Medical Center, Office of the CAO, 111 Michigan Ave, NW, Washington, DC 20010.

Are you or your child enrolled in the Longitudinal Study of Urea Cycle Disorders? Self  O Child  O Not enrolled

Are you enrolled in any other UCDC studies?  O Yes  O No  If yes, which study(ies)? __________________________

Do you find the newsletter:                What would you like to see in our next issue?

Difficult to read  O  O  O  O  O Easy to read  Other comments/suggestions:

Uninteresting  O  O  O  O Interesting

Not relevant  O  O  O  O Very relevant

Not worthwhile  O  O  O  O Very worthwhile

Did you go to our website to read the full articles whose abstracts appear in this newsletter?  O Yes  O No
The Urea Cycle Disorders Consortium (UCDC) is a team of doctors, researchers, and patient advocates, working together to improve the lives of individuals and families affected by urea cycle disorders through research and education. The consortium provides a way for patients to join doctors and researchers in developing new and better treatments for urea cycle disorders by participating in research studies. The greater the collaboration between doctors and patients, the more we can learn about urea cycle disorders. This important first step is necessary if we are to find new and better treatments.

The goals of the UCDC are to:

- Develop better treatments and a deeper scientific understanding of the causes of UCD.
- Understand how UCDs can cause brain damage and develop protection against this.
- Conduct clinical trials of promising new drugs for the treatment of UCD.
- Work with the National Urea Cycle Disorders Foundation, the UCD patient advocacy group, to understand the research priorities of the UCD community and to help patients who wish to be involved in research connect with doctors conducting UCD research.
- Construct and maintain resources with significant information for clinicians, researchers, and patients.
- Train a new generation of physicians to become experts in providing care for and treating those with UCD.

The Urea Cycle Disorders Consortium is part of the Rare Diseases Clinical Research Network (RDCRN) funded by the National Institutes of Health and through philanthropic support from the O’Malley Foundation, the Rotenberg Family Fund, the Dietmar-Hopp Foundation, and the Kettering Fund.

**Participating Sites**

**Children’s National Medical Center**  
(lead institution)  
Washington, DC

**Baylor College of Medicine**  
Houston, Texas

**The Children’s Hospital**  
Aurora, Colorado

**Children’s Hospital of Philadelphia**  
Philadelphia, Pennsylvania

**The David Geffen School of Medicine at UCLA**  
Los Angeles, California

**The Hospital for Sick Children**  
Toronto, Ontario, Canada

**Mount Sinai School of Medicine**  
New York, New York

**New England Center**  
(Children’s Hospital Boston with Yale School of Medicine)  
Boston, Massachusetts

**Oregon Health and Science University**  
Portland, Oregon

**Rainbow Babies and Children’s Hospital**  
Cleveland, Ohio

**Seattle Children’s Hospital**  
Seattle, Washington

**University Children’s Hospital**  
Zurich, Switzerland

**University of Heidelberg**  
Heidelberg, Germany

**University of Minnesota Amplatz Children’s Hospital**  
Minneapolis, Minnesota

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[www.RareDiseasesNetwork.org/ucdc](http://www.RareDiseasesNetwork.org/ucdc)