Issue 5 Winter 2021

UCDC Update

Newsletter of the Urea Cycle Disorders Consortium

Photograph taken during a virtual UCDC conference.

The events of 2020-2021 required all of us to rethink how we live, work and interact with one another. We adjusted our schedules for unexpected school closings, reorganized our homes to make room for makeshift offices, and even found inventive ways to connect with friends and family when we could not be near them. The Urea Cycle Disorders Consortium has made changes as well.

As we continue our important work for UCD patients and their families, the way we operate may look a little different. Our largest study that follows the lifelong medical history of UCD participants now offers remote consenting and telehealth visits, which allows participants to return their consent forms by mail and attend virtual study visits over the internet.

The 5th International Symposium on Urea Cycle Disorders also took place virtually. Our international symposiums are hosted every four years in partnership with the International Congress of Inborn Errors of Metabolism (ICIEM) and usually take place as in-person events. Since the symposium was held online this year, it was attended by rare disease experts from around the world, including those from underrepresented countries who could not previously participate. Some changes will be here to stay as they improve access to research and networking opportunities for investigators and participants.

Despite these unforeseen circumstances, our focuses remain the same: to better understand the causes and symptoms of UCDs and make advances in its treatment. We thank you for your contributions to UCD research and we hope the best for you, your family and all of us in the years to come.

- ***The Urea Cycle Disorders Consortium***

Neuropsychological Testing for the Longitudinal Study

Neuropsychological testing for the longitudinal study is ongoing. Here is a summary of the type of testing conducted and why it is important for the UCD community.

- Routine evaluation and testing associated with new and sudden changes in function
- Pre and post testing for liver transplant patients
- Testing conducted every two years for children and adults up to 26 years old; once for adults over 26 years old
- New testing capabilities could be quicker and more convenient
- The information collected allows us to:

  - Learn more about the impact of UCDs on neurocognitive functioning
  - Measure effectiveness of treatments
  - Follow the short and long-term effects of UCDs on neuropsychological functioning
  - Provide schools, educators and parents with information about kids with UCDs

If you think you are due for an evaluation, please contact the study coordinator at your enrollment site.

We welcome your feedback!

Please contact:
Jennifer Seminara
Urea Cycle Disorders Consortium
jseminar@childrensnational.org

Cindy Le Mons
National Urea Cycle Disorders Foundation
cindy@NUCDF.org.

What's Inside

Announcement

In 2019, Susan A. Berry, MD joined the board of directors for the National Organization for Rare Disorders (NORD), an independent nonprofit organization that represents millions of Americans with rare diseases.

Dr. Berry is the Division Director for Genetics and Metabolism in the Department of Pediatrics at the University of Minnesota and the principal investigator at the University of Minnesota for UCDC studies.

Developing Interactions with Industry in Rare Diseases: Lessons Learned and Continuing Challenges

Authors: Berry SA, Coughlin CR 2nd, McCandless S, McCarter R, Seminara J, Yudkoff M, LeMons C.

Publication: Genetics in medicine: official journal of the American College of Medical Genetics. 2020 January;22(1):219-226. PMID: 31337884; PMCID: PMC6944635

Key Point: The Urea Cycle Disorders Consortium partners with clinicians, patients, the National Institutes of Health (NIH), and pharmaceutical companies with a primary goal of increasing the development of therapeutics that improve patient outcomes for persons affected with a UCD.

The NIH established the Rare Diseases Clinical Research Network to address the unique challenges of performing research on rare diseases. The UCDC was one of the original ten consortia established. Based in part on financial incentives associated with the Orphan Drug Act of 1983 (a United States law that helped catalyze the development of drugs for rare diseases), biopharmaceutical and investment entities have an intense interest in engaging with rare disease research consortia like the UCDC, which have compiled potentially valuable longitudinal data characterizing outcomes in a relatively large number of affected individuals. Natural history data from the longitudinal study are invaluable not only for the many exploratory studies conducted by the UCDC, but also to industry partners seeking to develop new therapeutics to improve the lives of UCD patients and ultimately a cure.

This publication discusses the ways in which the UCDC navigates industry relationships in the pursuit of developing therapeutics for UCD patients. For example, the UCDC has developed a method for evaluating partnerships with private entities, established an Industry Relations Committee in 2015 to develop guiding principles, a policy and procedures for interacting with industry (including protection of data privacy), and managing investigator conflict of interest. By building a framework for industry partnerships that guides us in resolving inevitable challenges, the UCDC can pursue novel and promising collaborations that can lead to breakthroughs in treatment for patients.

Helpful Terms

Abnormal: Uncommon

Accumulation: The build-up of a substance.

ASA: Argininosuccinic aciduria

ASLD: Argininosuccinate lyase deficiency

ASS1D/Citrullinemia/Citrullinemia Type 1: Argininosuccinate synthetase deficiency

Chronic: A situation or disease that lasts for a long time.

CNS (central nervous system): The part of the nervous system that has the brain and spinal cord.

Deficiency: A lower amount than necessary for functioning.

Enzyme: Proteins produced by cells in the body that assists the body's processes.

Glycogen: a substance similar to starch that stores energy in the body.

Hepatic: Concerning the liver.

Hyperammonemia: Increased levels of ammonia in the blood.

Locus Coeruleus (LC): An area in the brain that signals stress.

OTCD: Ornithine transcarbamylase deficiency

Plasma: Liquid part of the blood in which blood cells are held.

Seizures: A temporary change in brain performance due to abnormal electrical activity of specific cells that can cause muscle contractions, lowered level of consciousness and other symptoms.

Threshold: Level reached that starts a reaction.

Urea: A product of protein breakdown of amino acids that leaves the body through urine.

ASL Metabolically Regulates Tyrosine Hydroxylase in the Nucleus Locus Coeruleus

Authors: Lerner S, Anderzhanova E, Verbitsky S, Eilam R, Kuperman Y, Tsoory M, Kuznetsov Y, Brandis A, Mehlman T, Mazkereth R; UCDC Neuropsychologists; McCarter R, Segal M, Nagamani SCS, Chen A, Erez A.

Publication: Cell Reports. 2019 Nov 19;29(8):2144-2153.e7. PMID: 31747589; PMCID: PMC6902269

Key Point: Individuals with argininosuccinate lyase deficiency (ASLD) are at risk for developing neurobehavioral and cognitive deficits, including attention deficits, increased seizure activity, and high blood pressure in response to stress, even without documented hyperammonemia.

The researchers developed a laboratory mouse model with ASL deficiency in specific regions of the brain and showed that argininosuccinate lyase (ASL) is required for the normal function of the nucleus locus coeruleus (LC) in the brain. LC is the main source of norepinephrine in the brain (an important chemical messenger in the brain and a stress hormone). Loss of ASL in the LC results in low amounts of nitric oxide (NO) which leads to the reduced amount and activity of tyrosine hydroxylase (TH), an enzyme needed to produce dopamine and norepinephrine. The mice with ASL deficiency in LC showed decreased amounts of dopamine and norepinephrine in the brain, displayed higher blood pressure, increased motor activity, and increased sensitivity to develop seizures. Treatment of these mice with donor NO resulted in lower blood pressure and less seizure activity.

Behavioral data previously collected from the Longitudinal Study of UCDs (Urea Cycle Disorders) conducted by the Urea Cycle Disorders Consortium showed 55% of participants with ASLD displayed lower attention spans during study visits, compared to 39.4% of participants with another UCD—argininosuccinate synthase deficiency (ASS1D/Citrullinemia). The results were similar for participants who did not have any documented episodes of hyperammonemia, which can affect behavior and cognition. Eighteen percent of participants with ASS1D without documented hyperammonemic events self-reported lower attention spans, compared to 54% of participants with ASLD. More research into the unique neurocognitive characteristics of ASLD will help improve treatment and management.

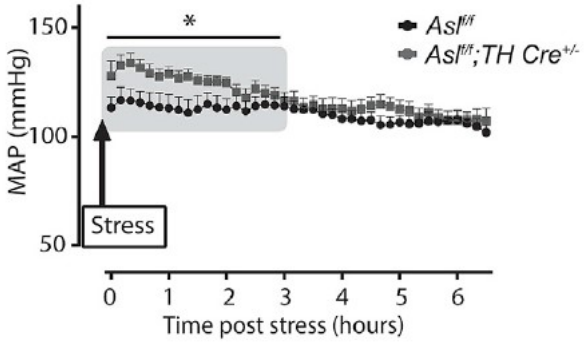

Figure 1: Shows the ASL deficient mice (top line) have significantly higher mean arterial pressure (MAP), or blood pressure, after experiencing stress. The stressful event was the introduction of unfamiliar mice.

Impact of Diagnosis and Therapy on Cognitive Function in Urea Cycle Disorders

Authors: Posset R, Gropman AL, Nagamani SCS, Burrage LC, Bedoyan JK, Wong D, Berry GT, Baumgartner MR, Yudkoff M, Zielonka M, Hoffmann GF, Burgard P, Schulze A, McCandless SE, Garcia-Cazorla A, Seminara J, Garbade SF, Kölker S; Urea Cycle Disorders Consortium and the European Registry and Network for Intoxication Type Metabolic Diseases Consortia Study Group.

Publication: Ann Neurol. 2019 Apr 24. PMID: 31018246; PMCID: PMC6692656

Key Point: Early detection by newborn screening and subsequent early liver transplantation appear to offer greater cognitive protection in UCD. Individuals diagnosed with UCD after having symptoms scored lower in cognitive testing than persons with UCD who were diagnosed prior to having symptoms. In this study, no single nitrogen-scavenger medication was found to be associated with better cognitive outcomes when compared to other nitrogen scavenging agents.

As intellectual and developmental disabilities are common in individuals diagnosed with urea cycle disorders (UCD), the purpose of this study was to evaluate the impact of diagnostic and treatment methods on cognitive outcomes such as thinking, reasoning, remembering, imagining, and learning. Results from neurocognitive testing of 503 individuals with UCD enrolled in the Longitudinal Study of UCD conducted by the UCD Consortium (UCDC) and the European Registry and Network for Intoxication Type Metabolic Diseases (E-IMD) from 2006 to 2016 were studied.

IQ scores less than 70, indicating intellectual disability, were associated with UCD type and early disease onset. The height of initial peak plasma ammonium level was associated with poorer neurocognitive outcomes in proximal UCDs (CPS1, OTCD). Individuals with citrullinemia (argininosuccinate synthetase deficiency, ASS1D) and argininosuccinate lyase deficiency (ASLD) who were identified by newborn screening but did not have symptoms at diagnosis had better outcomes than those diagnosed after having symptoms. Additionally, early liver transplantation appeared to be beneficial.

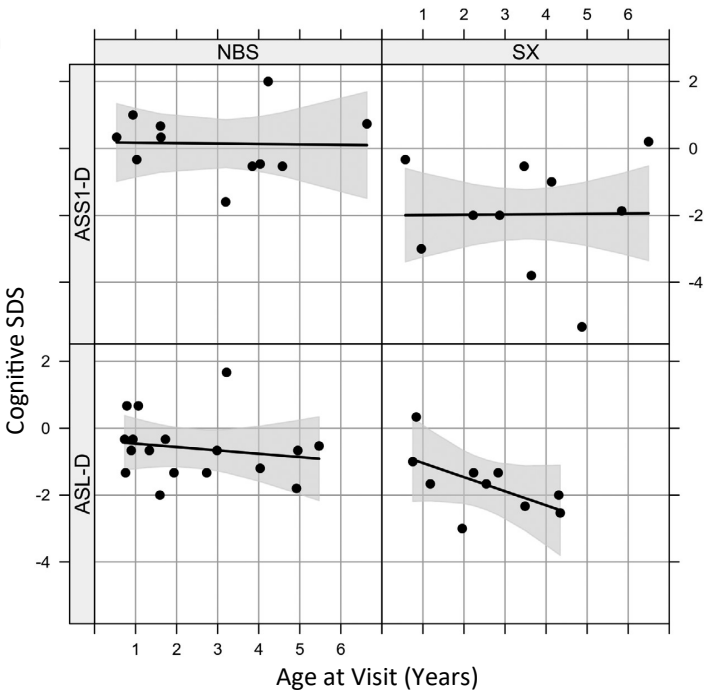

Figure 2: Compares the cognitive outcomes of children diagnosed with ASS1-D and ASL-D during newborn screening (NBS) or after symptom presentation (SX). NBS improved cognition outcomes for both ASS1-D and ASL-D.

Early Prediction of Phenotypic Severity in Citrullinemia Type 1

Authors: Zielonka M, Kölker S, Gleich F, Stützenberger N, Nagamani SCS, Gropman AL, Hoffmann GF, Garbade SF, Posset R; Urea Cycle Disorders Consortium (UCDC) and the European Registry and Network for Intoxication type Metabolic Diseases (E-IMD) Consortia Study Group.

Publication: Ann Clin Transl Neurol. 2019 Sep;6(9):1858-1871. Epub 2019 Aug 30. PMID: 31469252; PMCID: PMC6764635

Key Point: A new enzyme activity testing method for argininosuccinate synthetase 1 could help predict the course and severity of citrullinemia type 1.

Citrullinemia type1(ASS1D), also known as argininosuccinate synthase deficiency (ASS1D), is an inherited UCD that is detectable by newborn screening. The severity of the disease is variable, with health outcomes ranging from dangerous levels of hyperammonemic brain damage to mild, unnoticeable symptoms. Infant mortality rate for this disease has remained high over the decades despite the implementation of early treatment interventions.
In this study, researchers evaluated a new test that could possibly predict the severity of ASS1D , based on the activity level of the enzyme argininosuccinate synthetase 1 (ASS1), which has been shown in previous studies to predict the severity of other inborn errors of metabolism.

Participant data was collected from the Longitudinal Study of UCD conducted by the Urea Cycle Disorders Consortium (UCDC) and the European Registry and Network for Intoxication Type Metabolic Diseases (E-IMD).
The researchers used a newly established assay to measure enzymatic activity of ASS1. The results showed that participants with ASS1D with ASS1 activity at 8.1% or lower experienced more frequent and severe hyperammonemic events and poorer cognitive function than participants with ASS1 activity above 8.1%. Additionally, participants with 26.6% or lower ASS1 activity had participated in special education programs, and those with 19.3% or lower ASS1 activity suffered more often from movement disorders. Participants with 4.8% or lower ASS1 activity were more likely to undergo liver transplantation. These results suggest that this enzymatic activity method could be useful in the clinical outcome prediction.

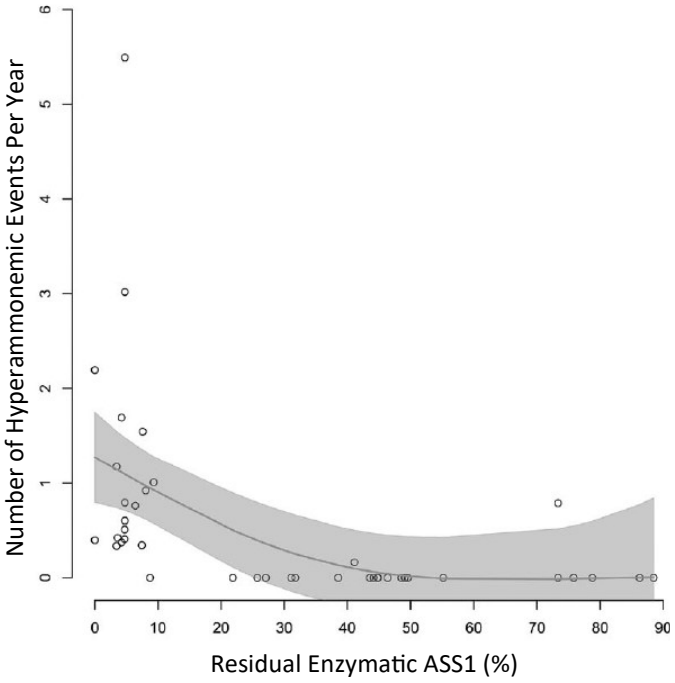

Figure 3: Shows ASS1 activity can indicate the number of hyperammonemic events (HAs). Each point represents a subject, the number of HAs the subject experienced in a year and their level of ASS1 activity.

Chronic Liver Disease and Impaired Hepatic Glycogen Metabolism in Argininosuccinate Lyase Deficiency

Authors: Burrage LC, Madan S, Li X, Ali S, Mohammad M, Stroup BM, Jiang MM, Cela R, Bertin T, Jin Z, Dai J, Guffey D, Finegold M, Nagamani S, Minard CG, Marini J, Masand P, Schady D, Shneider BL, Leung DH, Bali D, Lee B.

Publication: JCI insight. 2020 February 27;5(4). PMID: 31990680; PMCID: PMC7101134

Key Point: Individuals diagnosed with argininosuccinate lyase deficiency (ASLD) have high rates of liver disease. Whereas, generally, increased blood levels of the liver enzymes alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are used as biomarkers of liver disease in the general population, these markers may not by themselves accurately reflect the extent of liver disease in ASLD. In this study, the researchers used special ultrasound technology and a new biomarker in blood to assess liver disease in ASLD.

In this study, researchers reviewed participant data from the Urea Cycle Disorders Consortium's (UCDC) Longitudinal Study that included all types of UCD. The data suggested that individuals with argininosuccinate lyase deficiency (ASLD) and arginase deficiency had a higher prevalence of liver injury as compared to other types of UCD. Researchers assessed liver disease in individuals with ASLD and a laboratory mouse model of ASLD. Around 37% individuals with ASLD had increased ALT levels. Some of the ASLD participants were noted to have increased liver stiffness but normal ALT and AST levels.

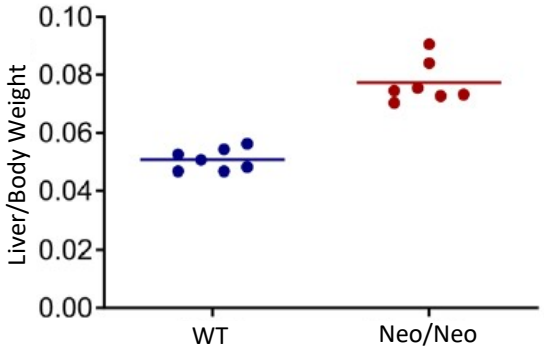

Figure 4: Liver weight in proportion to total body weight was increased in ASL mice (Neo/Neo) in comparison to non-ASL mice (WT), which is commonly referred to as liver enlargement.

The results showed that a quarter of the participants with normal ALT levels had abnormal liver imaging or testing. The ASLD study mice also developed chronic liver damage. These mice had excessive hepatic glycogen, liver enlargement, and increased ALT and AST levels. Hepatic glycogen accumulation has also been found in other types of UCD. More research is needed to identify the role of hepatic glycogen in UCD, as it is unknown whether it leads to, is the cause of, or is at all connected to damage in the liver. This study shows the need to identify additional biomarkers of liver damage in UCD.

Hepatic Arginase Deficiency Fosters Dysmyelination During Postnatal CNS Development

Authors: Liu XB, Haney JR, Cantero G, Lambert JR, Otero-Garcia M, Truong B, Gropman A, Cobos I, Cederbaum SD, Lipshutz GS.

Publication: JCI insight. 2019 September 5;4(17). PMID: 31484827; PMCID: PMC6777909

Key Point: Myelin is the fatty sheath surrounding nerves enabling nerve impulses to travel more rapidly. Arginase deficiency is a unique type of UCD that, unlike other UCD, damages the myelin of the brain and spinal cord causing loss of ambulation, intellectual disability, and progressive neurological decline. Neonatal gene therapy in mice restored the arginase activity in the liver and reversed this damage.

Arginase deficiency is classified as a urea cycle disorder (UCD), as arginase is necessary in the breakdown of ammonia in the body. However, unlike other urea cycle disorders, hyperammonemia is uncommon with arginase deficiency. Complications that arise in this disorder such as paralysis, muscle stiffening, involuntary muscle contractions and overactive reflexes are also associated with cerebral palsy. Additionally, complications in arginase deficiency often occur later compared to other UCDs. In this study, researchers found that mice with arginase deficiency had abnormal myelin pattern in the brain and the spinal cord. Treatment of these arginase deficiency mice with arginase 1 gene therapy rescued these abnormal myelin patterns.

Due to its unique characteristics among urea cycle disorders, the researchers suggest arginase deficiency be categorized as a leukodystrophy, a group of rare metabolic genetic disorders that affect the brain and spinal cord. This study did not label the cause of muscle and nerve failure within the disorder, yet supports the importance of ongoing neonatal screening, early intervention to normalize arginase production in the body. They also suggest that early postnatal liver-based gene therapy may be of use in preventing neurological abnormalities.

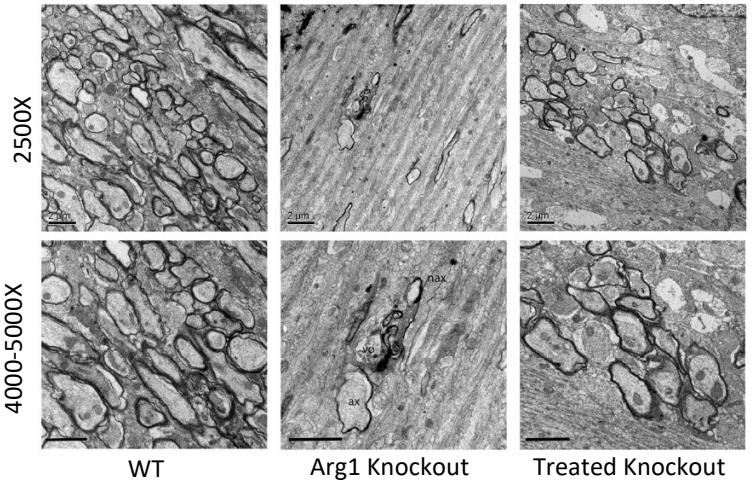

Figure 5: Arginase deficient (Arg1 Knockout) mice had decreased myelin density with abnormal pattern in the brain compared to normal mice (WT). Arginase deficient mice treated with UCD therapy (Treated Knockout) had more myelin compared to untreated Arginase deficient mice and more normal myelin pattern. The second row of images is a magnification of the first row.

From Genotype to Phenotype: Early Prediction of Disease Severity in Argininosuccinic Aciduria

Authors: Zielonka M, Garbade SF, Gleich F, Okun JG, Nagamani SCS, Gropman AL, Hoffmann GF, Kölker S, Posset R; Urea Cycle Disorders Consortium (UCDC) and the European Registry and Network for Intoxication type Metabolic Diseases (E-IMD) Consortia Study Group.

Publication: Human mutation. 2020 May;41(5):946-960. PMID: 31943503; PMCID: PMC7428858

Key Point: A new enzyme activity testing method for argininosuccinate lyase (ASL) could help predict the course and severity of argininosuccinic aciduria (ASA).

Argininosuccinic aciduria (ASA), caused by a deficiency in argininosuccinate lyase (ASL), is one of the more common urea cycle disorder subtypes. ASA has a wide range of symptoms ranging from mild disease to individuals with significant neurocognitive deficiencies. In this study, researchers analyzed previously collected patient data and correlated these with a new method of enzymatic testing for ASL to determine if the activity level of ASL was a reliable predictor of disease severity. The data was collected from the Longitudinal Study of UCD conducted by the Urea Cycle Disorders Consortium (UCDC) and the European Registry and Network for Intoxication Type Metabolic Diseases (E-IMD). The results showed that individuals with ASA with 8% or less ASL activity had higher initial ammonia levels and more frequent hyperammonemic episodes per year, and those with 8.7% or less ASL activity had increased liver damage. Overall, older ASL patients performed worse than younger ASL patients, which points to the possibility of chronic cognitive deterioration. The difference was more pronounced for those with ASL activity below 24.3%, suggesting additional underlying factors that affect cognition below a certain level of ASL activity. Based on the outcomes of this and previous studies, there is a possibility that ASL activity levels could help caregivers predict disease severity in ASA patients and inform the development of more effective, individualized treatments.

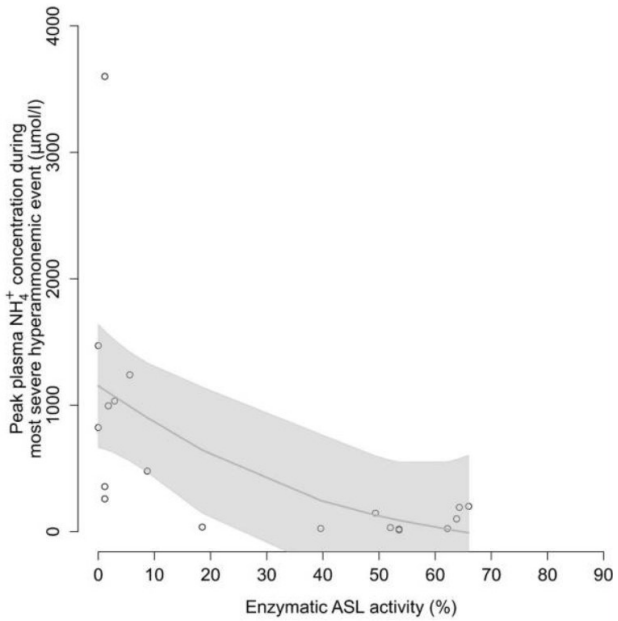

Figure 6: The mice with lower ASL activity had higher peak blood ammonia levels during their most severe hyperammonemic events. Each point represents an individual mouse.

Ongoing Studies

5101: Longitudinal Study of UCDs
Long-term observation of the impact of UCDs on physical and neurological functioning, the relationship between health indicators and disease severity and the efficiency of UCD therapies.

5111: Orphan Europe Carbaglu® Surveillance Protocol In Collaboration with the Longitudinal Study of Urea Cycle Disorders
A 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 acute hyperammonemia due to N-acetylglutamate synthase (NAGS) deficiency.

5113: Biomarkers of Neurological Injury and Recovery in Urea Cycle Disorders
Study of how UCDs affect thinking, body chemistry and brain structure using magnetic resonance imaging (MRI) and behavioral testing.

Do You Want to Learn More?

Visit our website for more information about recruitment, participating clinical sites and the overall goals of the UCDC!

www1.rarediseasesnetwork.org/cms/ucdc

New Studies

5119: Electrographic Seizures in Hyperammonemia
Investigates the presence of electrographic seizures during hyperammonemic events and if seizure intensity is connected to abnormal MRI findings, the development of epilepsy and neurological damage.

5120: Noninvasive Biomarkers of Hepatic Fibrosis in UCDs
Determines if non-invasive procedures—procedures that do not require instruments to enter the body—and health measures can indicate increased risk for liver stiffness. Also looks at how abnormal health measures affect the risk of liver stiffness among UCD individuals.

5121: Neurodevelopmental Assessments in Urea Cycle Disorder Consortium Longitudinal Study: Comparison of Standard (Traditional) Neuropsychological Battery and NIH Toolbox
Compares the NIH Toolbox, a computerized system of neuropsychological testing created by the National Institutes of Health (NIH), to standard neuropsychological testing currently used in UCDC studies. Also assesses how well the Toolbox is received by participants and testing administrators.

5122: Hepatic Histopathology in UCDs
Analyses past and present data to estimate the proportion of UCD individuals with liver disease, and compares the presence of liver disease across UCD subtypes and treatments, such as liver transplantation.

5123: Novel food photography method to measure dietary intake in patients with UCDs
Participants keep a visual food diary using a photography app . The accuracy of the calorie intake total calculated by the app is compared to manual calculation.