UCDC Update

Urea Cycle Disorders Consortium Newsletter

Issue 6 • Fall 2023

We are learning a lot about urea cycle disorders through your continued participation in research. We have more questions to answer.

The Longitudinal Study of Urea Cycle Disorders has been enrolling participants since 2006 and now has 943 participants enrolled at 15 sites in the United States, Canada, Germany and Switzerland.

We continue to learn more about urea cycle disorders from this dataset—the largest natural history study of UCDs ever conducted. Three of the five papers summarized in this newsletter use longitudinal study data; two of those studies combine data with a similar European natural history study.

It may seem that we have enough data given that we have been collecting information for 18 years, but we have many more questions that we would like to answer to be able to better diagnose and treat UCD patients. We have much more that we can learn from this valuable dataset to which many of you have contributed. As we analyze the data, we find that we have gaps that we need to try to fill to help us learn about cognitive differences that may be experienced by individuals with UCD.

Longitudinal Study participants: if you (or your child) are under 26 years old and have not had neuropsychological testing in the last two years, please reach out to the study coordinator at your site to schedule testing. If you have not been seen for a clinical visit in the last year, please reach out to a local study coordinator to discuss follow-up with your local metabolic physician or at the study site. A list of study coordinators at our 15 sites can be found on the last page of this newsletter. Your continued participation in the Longitudinal Study, and all of our UCD studies, is important; we appreciate your continued commitment to UCD research.

The Urea Cycle Disorders Team

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Inside This Issue

Helpful Terms

Abnormal: Uncommon

Asymptomatic: Not producing or showing symptoms.

Classification: Grouping items or people based on shared characteristics.

Cognitive: Related to thinking, reasoning and memory.

Deficiency/Deficit: A lower amount than necessary for functioning.

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

Frequency: Number of times an action occurs in a certain amount of time.

Hyperammonemia: Increased levels of ammonia in the blood.

Metabolic: Related to the process of using food to create energy in the body.

Motor: Movement

Neurological: Involving the brain, spine and nerves.

Non-invasive: Do not break the skin or enter the body.

Severity: Degree of symptoms. Low severity would have few, less serious symptoms, while high severity would have more and/or more serious symptoms.

Symptomatic: Producing or showing symptoms.

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

ASL Deficiency May Have Stronger Link to Neurological Disorders Than Other UCDs

ASL expression in ALDH1A1+ neurons in the substantia nigra metabolically contributes to neurodegenerative phenotype. Lerner S, Eilam R, Adler L, Baruteau J, Kreiser T, Tsoory M, Brandis A, Mehlman T, Ryten M, Botia JA, Ruiz SG, Garcia AC, Dionisi-Vici C, Ranucci G, Spada M, Mazkereth R, McCarter R, Izem R, Balmat TJ, Richesson R; Members of the UCDC, Gazit E, Nagamani SCS, Erez A. Hum Genet. 2021 Oct;140(10):1471-1485.

Click here to access the article.

In the urea cycle, enzyme argininosuccinate lyase (ASL) is required to convert waste-nitrogen to urea, which is released from the body in urine. Low ASL levels cause argininosuccinic aciduria, a urea cycle disorder that can present with hyperammonemia (HA)—increased ammonia in blood. Low ASL can also result in decreased nitric oxide production and nitric oxide deficiency has been connected to neurological disorders. In this study, the researchers analyzed data from the UCDC Longitudinal study to determine if individuals with argininosuccinic aciduria can have motor and cognitive deficits. The data showed that individuals with ASL deficiency experienced more tremors—a neurological disorder that causes involuntary shaking movements—than other UCD groups. In addition to examining data from the Longitudinal Study, researchers observed mice with low brain ASL levels and found that, although the mice did not suffer from hyperammonemia due to normal amounts of liver ASL, the mice displayed cognitive problems. Treatment of these mice with nitric oxide led to improvements in some aspects of behavior, which suggests that controlling nitric oxide levels may be beneficial for the treatment of some neurological disorders.

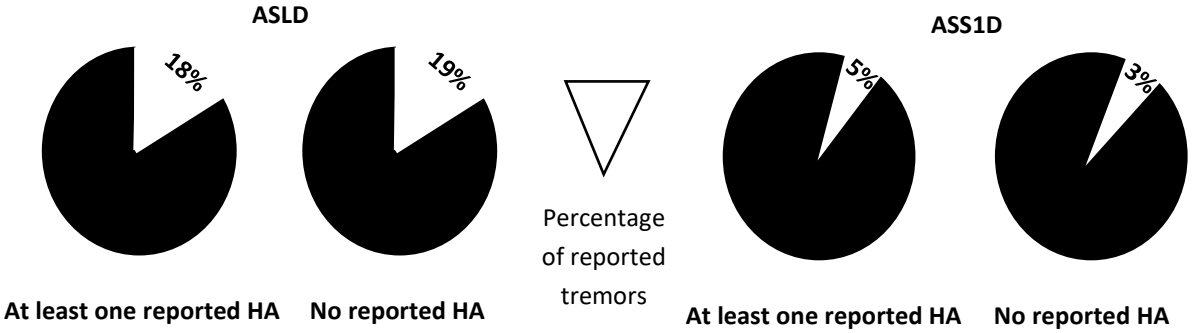

Figure 1: Pie charts show that ASLD individuals experienced more neurological disturbances than ASS1D individuals, with higher percentages of tremors in both hyperammonemic and non-hyperammonemic groups.

Non-Invasive Tools to Detect and Monitor Liver Disease Associated with UCDs

Biomarkers for liver disease in urea cycle disorders. Nagamani SCS, Ali S, Izem R, Schady D, Masand P, Shneider BL, Leung DH, Burrage LC. Mol Genet Metab. 2021 Jun;133(2):148-156.

Click here to access the article.

Due to increased awareness, earlier detection by newborn screening, and improvements in hyperammonemia therapies, life expectancy for individuals with urea cycle disorders has improved. This increased longevity encouraged healthcare providers to look at potential long-term complications in urea cycle disorders, such as liver disease. Liver diseases reported alongside urea cycle disorders include liver enlargement, inflammation, injury, failure, tumors, and fibrosis (tissue thickening and scarring). To date, there are no clear guidelines for screening and monitoring UCD patients.

In this Urea Cycle Disorders Consortium study, researchers investigated the potential of non-invasive tools for detecting liver injury and fibrosis. Researchers enrolled 28 adults and children with urea cycle disorders and performed the following tests: a standard liver ultrasound, a special ultrasound technique called shear wave elastography to measure liver stiffness, a marker of fibrosis, and special blood tests to assess liver inflammation and fibrosis. Forty-six percent of participants had an abnormal pattern on the standard liver ultrasound and 52% had increased liver stiffness. Analysis of blood tests showed a third of the participants had a result that represents an increased risk for liver fibrosis. This study highlights the high burden of liver disease in urea cycle disorders and the need for studies that explore new tools for identifying and monitoring individuals at risk for liver complications.

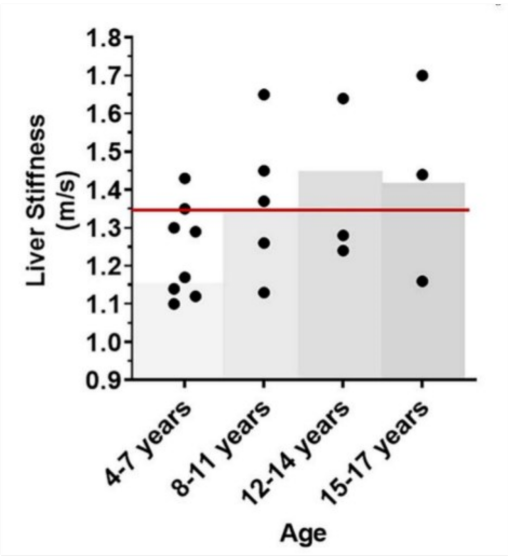

Figure 2: Eleven out of 19 pediatric (below the age 17) participants had higher liver stiffness than the general pediatric population, indicated by the gray boxes, which show the range of liver stiffness measurements per age group in the general pediatric population. The black dots are the individual liver stiffness measurements of the study participants. The red line represents the cutoff for normal liver stiffness in adults.

Using Brain Magnetic Spectroscopy (MRS) to Monitor Hyperammonemia

Clinical utility of brain MRS imaging of patients with adult-onset non-cirrhotic hyperammonemia. Stergachis AB, Krier JB, Merugumala SK, Berry GT, Lin AP. Mol Genet Metab Rep. 2021 Mar 13;27:100742

Click here to access the article.

In this study, researchers combined magnetic resonance imaging (MRI) and brain magnetic spectroscopy (MRS) to monitor five adults who developed hyperammonemia—elevated ammonia in blood. The study showed that high levels of brain glutamine on MRS may be associated with reversable neurological defects. However, with this limited number of participants, low levels of brain myoinositol on MRS was associated with the risk of developing irreversible neurological defects. Additionally, for two participants, brain glutamine and myoinositol levels were found to be more reliable than blood ammonia and glutamine levels in determining the successful clearance of ammonia from the body. The results of this study suggest that MRS scans can be of help in monitoring patients with urea cycle disorders who develop high ammonia levels and could help healthcare providers and families make informed decisions about clinical care.

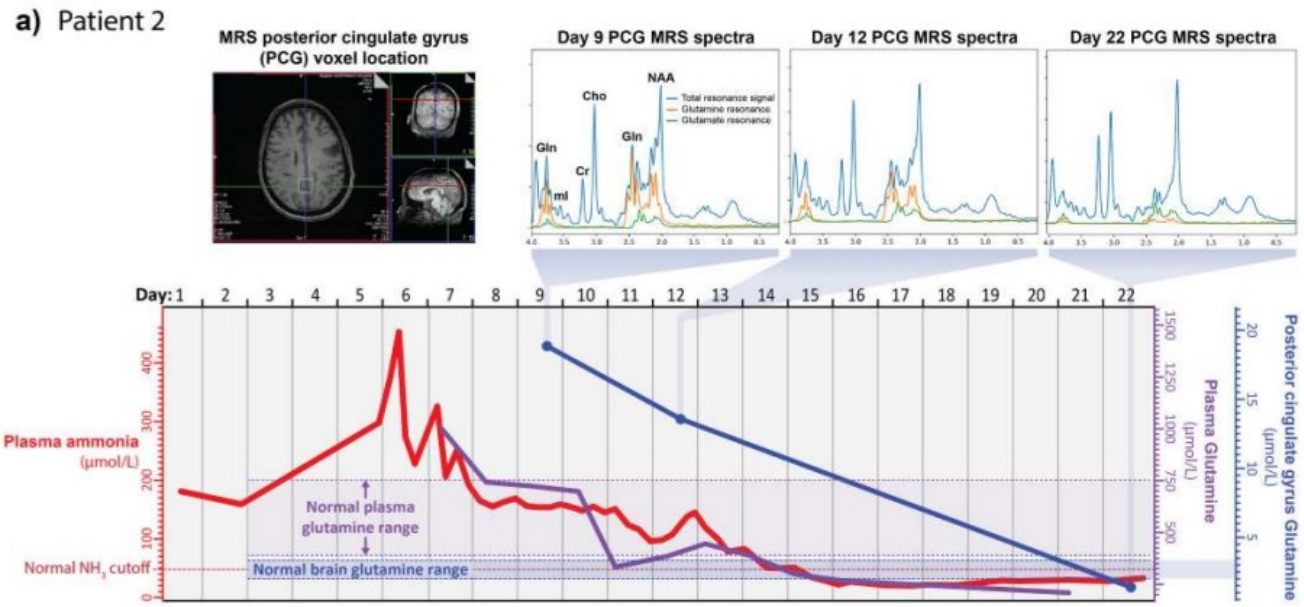

Figure 3: MRS image of brain region that, according to previous literature, demonstrates a sensitivity to increased glutamine. The bottom graph shows a time lapse of plasma ammonia (red), plasma glutamine (purple) and brain glutamine (blue) measurements.

Predicting Disease Severity in Males with Ornithine Transcarbamylase Deficiency (OTC-D)

Predicting the disease severity in male individuals with ornithine transcarbamylase deficiency.
Scharre S, Posset R, Garbade SF, Gleich F, Seidl MJ, Druck AC, Okun JG, Gropman AL, Nagamani SCS, Hoffmann GF, Kölker S, Zielonka M; Urea Cycle Disorders Consortium (UCDC) and the European registry and network for Intoxication type Metabolic Diseases (E-IMD) Consortia Study Group. Ann Clin Transl Neurol. 2022 Nov;9(11):1715-1726.

Click here to access the article.

Ornithine transcarbamylase deficiency (OTC-D), the most common urea cycle disorder, presents with a range of clinical severity, from asymptomatic to severe disease with significant neurological problems. Predicting the severity of disease in ornithine transcarbamylase deficiency is important for individualizing treatment. In this study, researchers developed a method to test the enzyme activity of ornithine transcarbamylase in order to help classify the severity of (OTC-D). For this study, the researchers used the clinical information and genetic makeup of 119 male participants enrolled in the UCDC Longitudinal study and the European registry and network for Intoxication type Metabolic Diseases (E-IMD) natural history study. Analysis showed that the participants' clinical outcomes were connected to their residual ornithine transcarbamylase enzyme activity; activity below or equal to 4.3% was associated with higher blood ammonia and mortality rates, and OTC activity below or equal to 16% was associated with more severe disease. Additionally, there was a connection between ornithine transcarbamylase activity and age at first symptoms, where participants with higher levels of activity showed clinical symptoms later in life than those with lower levels. Based on these findings, the researchers suggest complementing the current disease onset classification system, which determines ornithine transcarbamylase deficiency disease type by age of onset and symptomatic status, with a severity-adjusted classification system, that includes ornithine transcarbamylase activity.

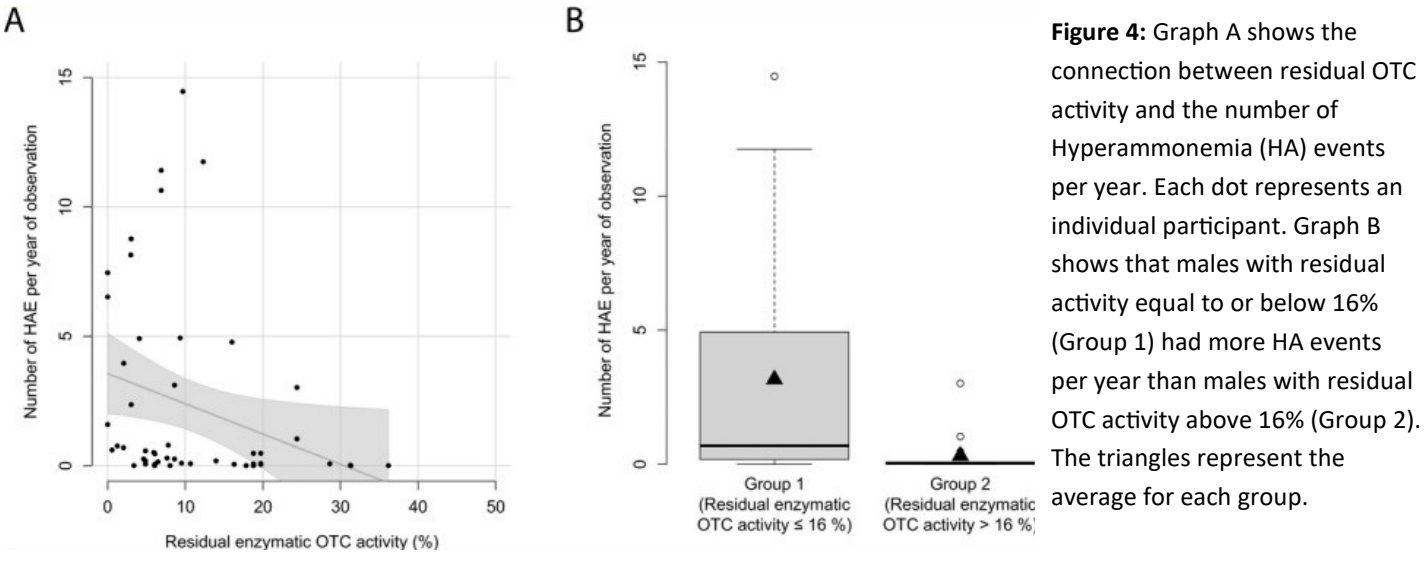

Figure 4: Graph A shows the connection between residual OTC activity and the number of Hyperammonemia (HA) events per year. Each dot represents an individual participant. Graph B shows that males with residual activity equal to or below 16% (Group 1) had more HA events per year than males with residual OTC activity above 16% (Group 2). The triangles represent the average for each group.

Evaluation of UCD Newborn Screening Based on Disease Severity

Severity-adjusted evaluation of newborn screening on the metabolic disease course in individuals with cytosolic urea cycle disorders. Posset R, Kölker S, Gleich F, Okun JG, Gropman AL, Nagamani SCS, Scharre S, Probst J, Walter ME, Hoffmann GF, Garbade SF, Zielonka M; Urea Cycle Disorders Consortium (UCDC) and the European registry and network for Intoxication type Metabolic Diseases (E-IMD) consortia study group.
Mol Genet Metab. 2020 Dec;131(4):390-397.

Click here to access the article.

Citrullinemia type 1 (CTLN1), caused by deficiency of enzyme ASS1, and argininosuccinic aciduria (ASA), caused by deficiency of enzyme ASL, are urea cycle disorders that have a wide range of symptom severity, from life-threatening hyperammonemia events during infancy to cognitive impairments and behavioral abnormalities observed later in life, even in the absence of hyperammonemia. In this study, researchers used the clinical information and genetic makeup of 115 CTLN1 and ASA participants enrolled in the UCDC Longitudinal study and the European registry and network for Intoxication type Metabolic Diseases (E-IMD) natural history study. The researchers created a severity classification system that associates the activity level of ASS1 and ASL with disease severity and predicts the frequency of hyperammonemia events: residual ASS1 and ASL enzyme activity below 8.1%(CTLN1) and 8.7% (ASA) is called predicted severe disease variant (high-severity) and residual activity equal to or above the cutoffs is called predicted attenuated disease variant (low-severity). This classification system was used to test the impact of newborn screening on the severity and frequency of hyperammonemia events. The results showed that newborn screening was associated with lower initial ammonia levels for both low and high severity disease classes, however, newborn screening was not associated with a lower frequency of hyperammonemia events for any class. This means that, while newborn screening is associated with lower levels of ammonia during the first hyperammonemic episode, it may not indicate the frequency of later hyperammonemic episodes. Additionally, researchers found that low-severity classes are overrepresented in newborn screening diagnoses. Being that the purpose of newborn screening is to diagnose UCDs before symptoms develop, it is difficult to determine if the therapy triggered by newborn screening diagnosis reduces disease severity or if the majority of those diagnosed by newborn screening have a naturally less severe course of disease. These findings suggest that the impact of newborn screening needs to be further evaluated with the use of similar disease severity classification systems.

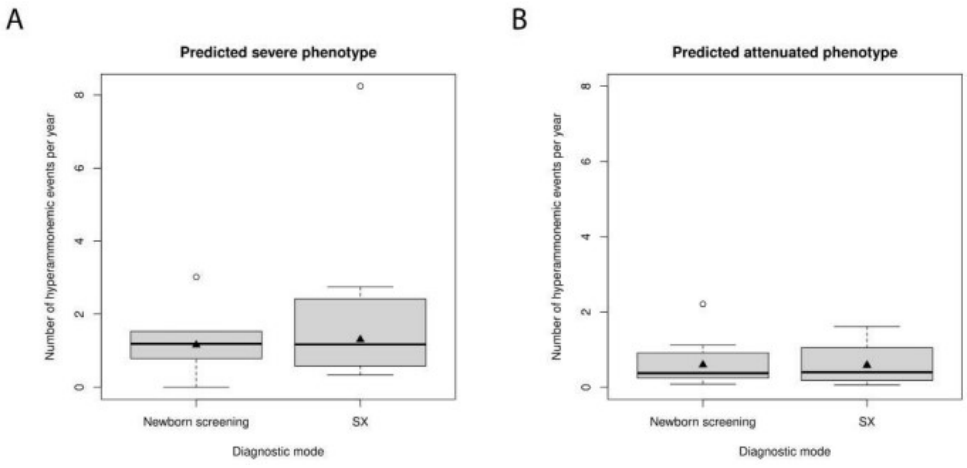

Figure 5: *Predicted severe phenotype* is classified as high-severity disease by the classification system and predicted *attenuated phenotype* is classified as low-severity. The graphs show that the frequency of Hyperammonemia (HA) events per year does not differ for high or low-severity classes regardless of diagnosis mode: newborn screening or later diagnosis due to symptoms (SX). The triangles represent the average number of HA events per group.

Other Things We Are Working On

Expanding role of proton magnetic resonance spectroscopy: Timely diagnosis and treatment initiation in partial Ornithine Transcarbamylase Deficiency. Sen K, Castillo Pinto C, Gropman AL. J Pediatr Genet. 2021 Mar;10(1):77-80. Epub 2020 Apr 23. Article Link

A case study of a young participant who was diagnosed with ornithine transcarbamylase deficiency (OTCD) after being screened with proton magnetic resonance spectroscopy (1H MRS).

Fifteen years of urea cycle disorders brain research: Looking back, looking forward. Sen K, Whitehead M, Castillo Pinto C, Caldovic L, Gropman A. Anal Biochem. 2022 Jan 1;636:114343. Epub 2021 Oct 9. Article Link

Highlights what has been found about the immediate and long-term neurological effects of hyperammonemia and the role of Electroencephalography (EEG) and Magnetic resonance imaging (MRI) in evaluation and recovery. Also showcases past research studies performed by the UCDC and future priorities.

Randomized and non-randomized designs for causal inference with longitudinal data in rare disorders. Izem R, McCarter R. Orphanet J Rare Dis. 2021 Nov 23;16(1):491. Article Link

Statisticians discuss the unique complexities of performing longitudinal studies on rare diseases, such as urea cycle disorders, and present design and analysis solutions.

Review of applications of near-infrared spectroscopy in two rare disorders with executive and neurological dysfunction: UCD and PKU. Khaksari K, Chen WL, Gropman AL. Genes (Basel). 2022 Sep 21;13(10):1690. Article Link

Reviews how near-infrared spectroscopy (fNIRS) is a useful non-invasive tool for screening and monitoring rare diseases with neurological dysfunction.

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