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LDN Research *Matters*

Pilot Project 5: The Role of *GLA* Gene Variants in Heart Disease

By Evelyn S. Redtree, M.S. and Raphael Schiffmann, M.D.

During the new funding cycle of the Lysosomal Disease Network, several pilot projects are being funded. (See page 14 for more information.) One of these pilot projects is "The role of *GLA* gene variants in heart and kidney disease." This is an extension of LDN Protocol # 6711 that was begun during the previous LDN funding cycle. Study #6711 was entitled "Expanded Screening for the Fabry Trait" and was conducted by Raphael Schiffmann, M.D. and S. Michael Mauer, M.D. The principal investigator of the new pilot project "The role of *GLA* gene variants in heart and kidney disease" is Dr. Raphael Schiffmann.

The *GLA* gene is the Fabry disease gene. Dr. Schiffmann hypothesizes that *GLA* variants, rarely considered in people with cardiovascular disease, may be relatively common and modifiable genetic risk factors. Mutation of the *GLA* gene is a strong risk factor for progressive renal disease, a variety of cardiac abnormalities, and ischemic stroke in both hemizygous males and heterozygous females.[1] It is estimated that patients with Fabry disease have up to a 12-fold

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In This Issue. . .

Meet Our Patient Advocacy Groups

The LDN considers itself lucky to have dedicated patient advocacy groups as members of the Network. This issue, we present with gratitude . . .

The Cystinosis Foundation

http://cystinosisfoundation.org/

The Cystinosis Foundation was the first non-profit charitable organization established to serve cystinosis patients and their families. The Cystinosis Foundation was founded in 1983 by Jean Hobbs-Hotz, after her one-year-old grandson, Joshua, was diagnosed with cystinosis. The Foundation's mission is to support and educate families and the medical community about cystinosis through the dissemination of educational literature, by funding research, by mentoring the establishment of patient support groups across the globe, and by organizing and hosting the International Cystinosis Congress. Jean Hobbs-Hotz continues to serve as the President of the Cystinosis Foundation.

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The Lysosomal Disease Network (U54NS065768) is a part of the NCATS Rare Diseases Clinical Research Network (RDCRN). RDCRN is an initiative of the Office of Rare Diseases Research (ORDR), NCATS, funded through a collaboration between NCATS and the National Institute of Neurological Disorders and Stroke (NINDS), and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Meet Our Patient Advocacy Groups

The Cystinosis Foundation

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"At the time of Joshua's diagnosis, there was no treatment and absolutely no public information about cystinosis. Our family made a monumental effort to find information about cystinosis and locate an expert. We were very fortunate to quickly locate Jerry A. Schneider, M.D., a pediatrician at the University of California at San Diego. I told Jerry I could not sit by and do nothing and he encouraged me to build a support group, which I did immediately," explained Jean Hobbs-Hotz. "We are grateful for the support and encouragement of Dr. Schneider and Dr. William A. Gahl over the past three decades.

"We hosted our first annual family conference in San Diego the very next year in 1984. I recall parents were thrilled to meet one another and share their experiences. Of course it was the first time the children had met another child with their condition, so the children had a wonderful time together," added Hobbs-Hotz.

President and Founder of the Cystinosis Foundation, Jean Hobbs-Hotz (left) and her daughter, Valerie Hotz, who serves as the volunteer Executive Director.

After 17 years of hosting the annual family conference in the U.S., in 2000 the Foundation's mission expanded internationally by hosting the International Cystinosis Congress on a bi-annual basis. "A major focus of our mission is to encourage others to build a support group in their own country. This is a tremendous service to families who receive a diagnosis and are immediately able to speak in their own language with another parent who can relate to what they are going through," said Hobbs-Hotz. The Cystinosis Foundation has empowered parents and individuals around the globe and mentored the establishment of patient support groups in 16 different nations including Australia, Belgium, Brazil, Canada, France, Germany, India, Ireland, Italy, Mexico, Netherlands, New Zealand, Spain, South Africa, United Kingdom and

By offering parental support in the form of information and referrals, newsletters, and Foundation-sponsored conferences for parents, the Cystinosis Foundation reaches out on a global basis to families who have a loved one with cystinosis. "Probably the greatest service our organization provides is to bring families together at our International Cystinosis Congress," said Valerie Hotz, Executive Director of the Cystinosis Foundation. Hotz is the aunt of Joshua, and has served as a volunteer since its founding. Hotz has been overseeing the expansion of the Foundation's mission to serve developing nations.

Gathered at the 8th International Cystinosis Congress in Manchester, UK, July 24-26, 2014, from left to right: Merle Mund, member of the Cystinosis Foundation Board of Directors; Valerie Hotz, Executive Director of the Cystinosis Foundation; Lee Knaus, member of the Cystinosis Foundation; Roy Forsyth, Chair of the Cystinosis Foundation of the UK; and Neil Sugden, member of the Cystinosis Foundation of the UK Board of Directors.

The Cystinosis Foundation and the Cystinosis Foundation of the UK collaborated to host the 8th International Cystinosis Congress. This bi-annual conference is the world's largest gathering of cystinosis patients and their families. The two and a half day agenda included presentations by scientific experts in cystinosis research, delightful team-building events, a walking tour of Manchester, and concluded with a gala dinner and dancing. Over 200 individuals from 16 different countries on four continents participated.

"Our conference program is unique and highly regarded by both our community of affected families and medical professionals. An international committee

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Meet Our Patient Advocacy Groups

The Cystinosis Foundation

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comprised of patients, families and medical professionals design our program agenda. The two and a half day conference always includes presentations by experts in the field of cystinosis research; opportunities for questions and answers; fun team-building events; an informal poster session that invites interaction between patients, families and medical experts; a gala dinner; and plenty of opportunities for making new friends," added Hotz. The 9th International Cystinosis Congress will convene summer 2016. Visit www.cystinosisfoundation.org for more information, or to submit a medical question to a cystinosis medical expert. You may also visit the Cystinosis Foundation on Facebook at www.facebook.com/cystinosis. Details about the 9th International Cystinosis Congress will be posted online as they become available.

The Cystinosis Foundation is a founding member of the National Organization of Rare Disorders (NORD), with Hobbs-Hotz having served as a founding Director of NORD–EURODIS, and the Genetic Alliance, two significant organizations that further the cause of those coping with rare disease. Valerie Hotz said, "We assisted EURORDIS in creating the cystinosis page for their *RareConnect.org* web site, an excellent resource that provides reliable information in five languages: English, French, German, Italian and Spanish." Visit: https://www.rareconnect.org/en/community/cystinosis.

The Cystinosis Foundation also strives to educate the medical profession and the general public about cystinosis. In 2013 the Foundation organized and sponsored families' visits to legislators on Capitol Hill to inform them about the needs of cystinosis patients and to encourage support of the NIH budget. In recent years the Foundation made educational presentations at the Italian Pediatric Nephrology Association meeting; the Brazil Pediatric Nephrology meeting, where it also hosted the Cystinosis Symposium; and the 2014 KDIGO (Kidney Disease Improving Global Outcomes) Cystinosis Controversies Conference in Lisbon, Portugal. Current efforts are focused on writing a children's book about cystinosis and its treatments.

The Cystinosis Foundation took the lead to fund research on important projects, including carrier status, development of the *CTNS* mouse model, neurocognitive research in cystinosis, and in the late 1990s provided grant funding in support of delayed-release cysteamine research. "These early investments in cystinosis research contributed to great strides in our understanding of this condition, to the development of treatments and helping to bring us where we are today. However, there remains much we do not know and especially much work needs to be done in the area of extra-renal complications in adult cystinosis patients," added Valerie Hotz. (Read "Check Your Knowledge of Lysosomal Diseases" beginning on page 6 of this issue, to learn more about cystinosis and its complications.)

BEYOND BORDERS
CYSTINOSIS FOUNDATION

Other Organizations:

Cystinosis Foundation UK
174 Corwen Road
Tilehurst
Reading, RG30 4TA United Kingdom
Phone #: 004-411-89414232
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Cystinosis Research Foundation
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Home page: http://www.cystinosisresearch.org

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LDN Research *Matters*

Pilot Project 5: The Role of *GLA* Gene Variants in Heart Disease

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increased risk of stroke compared to the general population, and the risk of developing kidney and cardiac disease is certainly much higher than that. Fabry disease incidence has been estimated at 1:117,000 live male births; however, when newborns are screened using Sanger sequencing, the frequency increases to 1:3,100.[2]

This pilot project has three primary aims: (1) to identify *GLA* variants in populations of patients with common heart disease; (2) to determine the clinical relevance of each *GLA* variant by examining urinary globotriaosylceramide (Gb_3) and α-galactosidase A activity in body fluids and tissues, and by estimating the frequency of each gene variant relative to the general population; and (3) to then institute specific therapy in appropriate patients, and follow treatment effects over time in those patients.

An innovation in Dr. Schiffmann's method of conducting this pilot project is his use of massive parallel sequencing of the entire *GLA* gene (exons and introns) in pooled genomic DNA samples. This new method allows a complete inventory of all *GLA* gene abnormalities in large groups of at-risk patients. Previously, studies used either measurement of α-galactosidase A activity, or traditional Sanger gene sequencing. Unfortunately these older methods can miss clinically significant *GLA* gene variants. In addition to *GLA* sequencing, all patients will have measurement of their urinary Gb_3 and assay of α-galactosidase A activity.

Inclusion criteria for this pilot project are: males and females over the age of 18 years with any cardiac abnormality. Exclusion criteria are: those unable or unwilling to give consent, or patients younger than 18 years of age. Previously, 1,227 heart disease patients were recruited from 5 hospitals and clinics in the Dallas, Texas area for Protocol #6711. These 1,227 patients did not have their DNA sequenced. These subjects, and newly recruited subjects from the same area, will be studied. All identified subjects with clinically relevant *GLA* variants will be offered genetic counseling and specific Fabry disease therapy. The effects of their therapy on appropriate clinical parameters will be assessed.

In addition to the support provided by the LDN, Protocol #6711 was supported by Amicus Therapeutics, Inc., Shire, plc and the Baylor Health Care System. Dr. Schiffmann emphasized his appreciation for Amicus Therapeutics, Inc.'s expressed intent to continue their support of this new LDN pilot project.

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Publications arising from LDN Protocol #6711:

R. Schiffmann, S. Forni, C. Swift, N. Brignol, X. Wu, D.J. Lockhart, D. Blankenship, X. Wang, P.A. Grayburn, M.R. Taylor, B.D. Lowes, M. Fuller, E.R. Benjamin, L. Sweetman, Risk of death in heart disease is associated with elevated urinary globotriaosylceramide. J Am Heart Assoc 3(1) (2014) e000394. PMCID: PMC3959711. Article freely available online at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3959711/.

Sanfilippo Syndrome Type B Clinical Trial of ERT Now Underway

Synageva BioPharma Corp., a biopharmaceutical company developing therapeutic products for rare disorders, announced on Jan. 26, 2015 that dosing with their investigational drug called SBC-103 in patients with mucopolysaccharidosis IIIB (MPS IIIB, also known as Sanfilippo syndrome type B) has begun, as part of

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Meet the Principal Investigators

Raphael Schiffmann, M.D.

Raphael Schiffmann. M.D., is Director, Institute of Metabolic Disease, Baylor Research Institute, Dallas, TX. He is also Clinical Professor, Texas A&M University Medical School College of Medicine.

Dr. Schiffmann's research primarily focuses on neurometabolic diseases and in particular, lysosomal diseases and leukodystrophies. He investigated the natural history, pathogenesis and treatment of Fabry disease. Dr. Schiffmann conducted pivotal studies that helped lead to the approval of enzyme replacement therapy for Fabry disease in 45 countries. He also investigated the pathogenesis of the neurological and neuropathological aspects of Gaucher disease and its response to enzyme replacement therapy and substance synthesis reduction therapy.

Raphael Schiffmann, M.D.

Dr. Schiffmann's studies on the neurogenetics of mucolipidosis type IV confirmed the clinical and biochemical homogeneity of this disease, providing an important step toward identifying the mucolipidosis IV gene. He discovered novel leukodystrophy syndromes, including Childhood Ataxia with Central Nervous System Hypomyelination (CACH; vanishing white matter disease; eIF2B related disease), ovarioleukodystrophy, and 4H syndrome. Dr. Schiffmann continues to be active in all of these research areas.

Selected Raphael Schiffmann, M.D. Publications:

R. Schiffmann, M.S. van der Knaap, An MRI-based approach to the diagnosis of white matter disorders. Neurology 72(8) (2009) 750-759. PMCID: PMC2677542. Article freely available at: http:// www.ncbi.nlm.nih .gov/pmc/articles/PMC2677542/

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Change in RDCRN Acknowledgement Language

Lysosomal Disease Network-funded investigators must include, in each publication whose underlying research project was funded in full or in part by the Lysosomal Disease Network, an acknowledgement of NIH funding. After stating that the work was supported by the Lysosomal Disease Network, the following language ***must*** appear:

"The Lysosomal Disease Network (U54NS065768) is a part of the NCATS Rare Diseases Clinical Research Network (RDCRN). RDCRN is an initiative of the Office of Rare Diseases Research (ORDR), NCATS, funded through a collaboration between NCATS and the National Institute of Neurological Disorders and Stroke (NINDS), and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)."

All investigators must also make sure their publication becomes published in PubMedCentral in a timely manner, whether their scientific journal submits it for them, or they perform that task themselves.

Check Your Knowledge of Lysosomal Diseases

How well do you know cystinosis?

By Evelyn S. Redtree, M.S.

Introduction to an Understanding of Cystinosis

Cystinosis, an autosomal recessive metabolic disease, is the result of a defect of molecular transport across the lysosomal membrane. Cystinosis is caused by any of a multitude of mutations to the *CTNS* gene, which is located at 17p13. *CTNS* encodes the lysosomal-membrane protein cystinosin, which transports cystine, a disulfide amino acid that serves an important structural role in many proteins. Cystine is a byproduct of protein degradation inside the lysosome; it needs to be transported across the lysosomal membrane into the cell's cytoplasm, for reduction into cysteine.[1] Once in the cytoplasm, cysteine can be further metabolized to form glutathione.[2] (For more about glutathione, read page 3 of the November 2014 issue of '**Indications**.') When this fails to occur, or occurs inadequately (as in the case of the presence of some residual cystinosin activity), cystine gradually accumulates inside the lysosomes in almost all cells and tissues, including (but not limited to) the brain, kidneys, thyroid gland, conjunctivae and corneas, liver, spleen, lymph nodes, intestines, rectal mucosa, muscle, bone marrow and macrophages. When the concentration of dissolved cystine inside lysosomes reaches saturation, cystine crystals precipitate out of solution and accumulate within the lysosome.

Fanconi syndrome occurs when the function of cells in proximal renal tubules is impaired, leading to abnormal amounts of carbohydrates and amino acids in the urine, excessive urination, and low blood levels of potassium, phosphates, and other electrolytes. Cystinosis is the most common identifiable cause of renal Fanconi syndrome in pediatric patients.[1] (Cystinosis is not the *only* known cause of Fanconi syndrome.)

The exact mechanisms of tissue damage in cystinosis are not yet fully understood.[3] Research has suggested that additional lysosomal functions are impaired in cystinosis, not only the transmembrane movement of cystine.[3] It is hypothesized that increased intracellular cystine profoundly disturbs cellular oxidative metabolism and glutathione status, leading to altered mitochondrial energy metabolism, autophagy, and apoptosis.[3]

Cystinosis Incidence

The estimated incidence is 1:100,000 to 1:200,000 live births.[2] There are approximately 500 extant reported cases in North America, and about 2,000 known cases worldwide.[4] The rarity of cystinosis presents a serious diagnostic challenge for physicians; therefore the true incidence and prevalence of cystinosis remains uncertain.

There are Three Classifications of Cystinosis

Nephropathic cystinosis is the most common form, comprising about 95% of all known cases.[2] Patients generally present before the age of 12 months with excessive urination, excessive thirst and failure to thrive caused by generalized proximal renal tubular damage. The excessive urination, with daily excretion of 2 to 6 liters of dilute urine, may lead to death from rapidly-progressing dehydration.[5] The excessive urination includes excretion of water, sodium, chloride, potassium, bicarbonate, calcium, amino acids, glucose, carnitine and low molecular weight proteins. A generalized aminoaciduria results in the excretion of amino acids at concentrations that are *10 times* the normal values.[5] Phosphaturia results in hypophosphatemic rickets.[5]

The kidneys of nephropathic cystinosis patients have a characteristic narrowing of the proximal renal tubules, or "swan-neck" deformity.[5] The swan-neck deformity develops early in the course of nephropathic cystinosis and appears to coincide with the development of Fanconi syndrome.[5] Following onset of the proximal tubulopathy, children with untreated nephropathic cystinosis have chronic interstitial nephritis, progressing tubular degeneration, endothelial proliferation in the glomeruli, multinucleated giant cells, and glomerular necrosis and hyalinization with arteriolar thickening, as the disorder progresses to end-stage renal disease at approximately 10 years of age.[5]

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Check Your Knowledge of Lysosomal Diseases

How well do you know cystinosis?

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In addition to the organs mentioned in the 'Introduction' on page 5, untreated nephropathic cystinosis signs can include, but are not limited to: pancreatic damage (resulting in exocrine and endocrine insufficiency); muscle involvement including pulmonary insufficiency, swallowing abnormalities, severe muscle wasting and vacuolar myopathy; hypercholesterolemia; retinopathy resulting in retinal blindness; vascular calcifications; diabetes mellitus; cerebral calcifications including basal ganglia and periventricular calcifications, often accompanied by cerebral atrophy; benign intracranial hypertension; short stature (greater than 2 standard deviations below the mean); thyroid gland fibrosis and hypothyroidism; nodular regenerating hyperplasia of the liver; and chronic intestinal damage that can lead to bowel perforation and/or peritonitis.[1,2,5,6] Additionally, photophobia is caused by corneal cystine crystals, which can be recognized by an experienced ophthalmologist from the approximate age of 12 months.[2]

As with many lysosomal diseases, less severe forms of cystinosis most likely form a disease continuum; nevertheless, two distinct subtypes have historically been emphasized in the literature: intermediate cystinosis, and ocular cystinosis.[5]

Intermediate cystinosis is also called "late-onset" or "juvenile" cystinosis, with disease onset mostly after the first decade of life.[2] It has the same clinical presentation as nephropathic cystinosis, but demonstrates a slower rate of progression.[2,5] The slower progression is the result of the presence of some residual cystinosin activity. Cystine crystals accumulate in these patients' corneas at a relatively slow rate.[2,5] They may retain their renal function into their 30s, and their statural growth is only moderately impaired.[5]

Ocular cystinosis, also known as non-nephropathic cystinosis, previously called "adult" or "benign" cystinosis, is characterized by the same ocular findings typical of nephropathic cystinosis, but is free of all other systemic manifestations.[2,5]

Treatment of Cystinosis

Prior to 1960, persons born with nephropathic cystinosis either died in infancy because of renal Fanconi syndrome, or they died in the first decade of life because of chronic glomerular failure.[1] In the late 1960s, advances in kidney transplantation dramatically increased the survival of patients with nephropathic cystinosis.[1] With this increased life span, the widespread effects upon non-renal tissues first became obvious.[1] (Originally, most non-renal organ involvement remained hidden because patients died so young.) Kidney transplantation remains an important treatment for persons who have cystinosis, as no available drug treatment completely prevents progressive renal damage.[1]

Therapy with cysteamine (β-mercaptoethylamine), an aminothiol, results in long-term depletion of lysosomal cystine.[5] Cysteamine was first introduced as a possible therapeutic agent to treat cystinosis in 1976.[2,7] In 1994, cysteamine bitartrate (Cystagon®, Mylan Pharma, Morgantown, WV, USA) was approved by the FDA and became the most widely used preparation of cysteamine.[2]

Early diagnosis is essential for successful treatment of nephropathic cystinosis.[5] For newborn infants in families having a known history of cystinosis, genetic testing, or measuring the cystine content of polymorphonuclear leukocytes, can identify those infants who have cystinosis, prior to the appearance of symptoms. This is the *ideal time* to begin treatment with cysteamine. Naturally, the best outcomes would result if all newborns underwent screening for cystinosis. If the condition is not swiftly identified and treated with cysteamine in infancy, chronic renal failure may develop at an early age, with the attendant need for dialysis and kidney transplantation.[5] Yet, misdiagnosis of cystinosis is a real problem because of the rarity of the disease and the lack of universal newborn screening for cystinosis. As in many other lysosomal diseases, the diagnostic odyssey can waste a great deal of time, thus delaying treatment—with catastrophic consequences.

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Check Your Knowledge of Lysosomal Diseases

How well do you know cystinosis?

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Cysteamine therapy has dramatically improved the prognosis for children with nephropathic cystinosis, but it is not a perfect treatment for all of the physical consequences of cystinosis, both renal and non-renal. If cysteamine therapy is started early, the prognosis for glomerular function is good; nevertheless, proximal renal tubular dysfunction still develops at an early age.[5] Clinical trials have also demonstrated that the use of cysteamine therapy beginning very early in life retards renal glomerular deterioration, and improves statural growth.[8,9] Diabetes mellitus, hypothyroidism, myopathy, and pulmonary dysfunction occur less frequently in cysteamine treated cystinosis patients who have been treated for a prolonged period of time.[1,5] Many long-term cysteamine treated patients have survived into their third decade without the need for renal transplantation.[5] After kidney transplantation, cysteamine is often still prescribed to prevent or attenuate the non-renal organ damage of cystinosis.[5]

Even when treated with cysteamine, the renal consequences of cystinosis require normal electrolyte replenishment with oral solutions of sodium bicarbonate, or the more palatable sodium–potassium citrate.[5] Oral calcium supplements may be required.[5] To prevent renal rickets, sodium phosphate and 1,25-dihydrotachysterol must be administered beginning in early childhood.[5] Carnitine replacement raises low plasma carnitine levels.[5] To ensure adequate nutrition some treatment centers place gastrostomy tubes, which also assists drug administration.[5] Although growth hormone is not an obligate deficiency in patients with cystinosis, treatment with growth hormone permits a growth spurt that can allow patients to achieve and maintain normal height for their age.[5] Hypothyroidism is controlled with levothyroxine therapy, and testosterone replacement may be helpful for selected men with hypogonadism.[5] If renal failure occurs, patients are treated with peritoneal dialysis or hemodialysis until a renal allograft can be transplanted.[5]

Approximately 14 percent of cystinosis patients are unable to tolerate cysteamine therapy because of nausea and vomiting.[5] Even in patients that can tolerate it, nausea is a common side effect.[5] Systemic administration of cysteamine does not prevent formation of corneal cystine crystals, so patients use topical cysteamine eye drops which must be applied hourly during waking hours. In 2013 Cystaran™ (cysteamine ophthalmic solution) 0.44% (Sigma-Tau Pharmaceuticals, Inc., Gaithersburg, MD, USA), was approved by the FDA for the treatment of corneal cystine crystal accumulation in patients with cystinosis.

The dosing regimen for cysteamine is administration every 6 hours; ideally, it should also be administered during the night. Such a dosing scheme results in an unhealthful and extremely difficult compliance burden for patients and/or their caregivers. Yet, if this dosing regimen is not adhered to, inadequate depletion of cystine results. Over the long term inadequate depletion of cystine leads to the devastating physical effects of cystinosis. Readers can ponder the implications of neither the patient, nor their caregiver(s), ever obtaining more than 6 consecutive hours of sleep. Multiple studies have documented most cystinosis patients' inability to maintain optimal disease control with immediate-release cysteamine, with subsequent progressive chronic kidney disease.[5,6] In a study by Cochat et al.[10] the rate of *non-adherence* to the every-6-hours dosing regimen was estimated to be 62%. In a study by Brodin-Sartorius et al.[6] the leukocyte cystine level was *optimal* in only 28% of the cysteamine treated patients.

Problems with cysteamine include that as an aminothiol, cysteamine has the marked odor and taste of thiols —the "rotten egg" smell. This odor binds to patients' oral mucosa and dental fillings, resulting in severe halitosis.[2,5,6] It eventually permeates their bodies, giving them a strong "rotten egg" body odor. Readers can ponder the impact of this side-effect upon the growing infant's and child's family and social relationships, social development, and occupational prospects as an adult.

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Check Your Knowledge of Lysosomal Diseases

How well do you know cystinosis?

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In 2013 an enteric-coated preparation of delayed-release cysteamine bitartrate (Procysbi™, Raptor Pharmaceuticals Inc., Novato, CA, USA) was approved by the FDA and European Medicines Agency for treatment of cystinosis. This formulation of microspheronized, micro-encapsulated beads of cysteamine bitartrate allows extended pharmacokinetics and pharmacodynamics that result in a dosing regimen of every **12 hours** instead of every 6 hours. The delayed release allows the cysteamine to enter the small intestine before it is absorbed. This has resulted in a smaller dose being needed to achieve the same level of cystine depletion as is achieved by the correct dosage of immediate-release cysteamine.[11]

Under a controlled, prospective protocol, a clinical trial achieved optimal control of cystinosis (defined as maintaining the mean white blood cell content of cystine at <1 nmol of half-cystine/mg protein), with preservation of kidney function, stable somatic growth and stable body mass index.[11] Participants' quality of life significantly improved in social function, school function, and in total function as patients switched to delayed-release cysteamine compared with immediate-release cysteamine.[11] These changes were maintained for the entire 24-month period of the trial.[11] For cystinosis patients who can afford it, this provides the opportunity for maintaining optimal control of their disease without sacrificing adequate consecutive hours of sleep.

Future Possible Treatments

A *prodrug* is a precursor chemical compound of a drug. It is a medication that is administered in a pharmacologically inactive form, which is subsequently converted to an active form through a normal metabolic process. This reduces adverse or unintended effects of a drug. Prodrugs are being researched in order to diminish the bad taste and smell of cysteamine, and to increase its half-life in order to lengthen the interval between doses. Some prodrugs of cysteamine have been tested in vitro;[12,13] none decrease intracellular cystine levels as effectively as cysteamine, and none have yet warranted in vivo testing.[12,13]

Bone marrow transplantation and gene therapy for cystinosis are still in the early research phase.

Prognosis for Treated Cystinosis

Now, as children with treated cystinosis survive into adulthood, the true disease burden has become increasingly clear.[1] For patients who are homozygous for the most damaging *CTNS* mutations, the cystinosis mortality rate in young adulthood approximates one third, and death generally occurs before 30 years of age.[1] For the two-thirds of cystinosis adult patients who survive longer, the cumulative effects upon the non-renal organs can also be devastating. Seldom does such a patient reach their late 30s without a major, life-altering medical complication of cystinosis.[1] Swift, early diagnosis and prompt, fully-compliant cysteamine treatment is essential for avoiding, attenuating, or substantially delaying renal and non-renal consequences of cystinosis.

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Learn More . . .

Online Mendelian Inheritance in Man – Nephropathic Cystinosis: http://www.omim.org/entry/219800?search=219800&highlight=219800

Cure Cystinosis International Registry's Web site: https://cystinosis.patientcrossroads.org/. To learn more about the registry and its importance in furthering cystinosis research; and to learn how to join the registry, visit: https://cystinosis.patientcrossroads.org/en/home/understanding-your-participation.html

National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) -- more information about their Pediatric Kidney Disease Program is at: http://www.niddk.nih.gov/research-funding/research-programs/Pages/pediatric-kidney-disease-.aspx

NIH's Office of Rare Diseases Research information pages about cystinosis:
1. http://rarediseases.info.nih.gov/gard/9755/nephropathic-cystinosis/resources/1
2. http://rarediseases.info.nih.gov/gard/9756/cystinosis-ocular-nonnephropathic/resources/1

Cystinosis Research Network offers hyperlinks to patient and family resources, cystinosis support groups, pertinent cystinosis articles, and health insurance information on their homepage at: https://cystinosis.org/

Cystinosis Research Foundation's homepage is at: http://www.cystinosisresearch.org/

Hot Off the Press

Selected Recent Publications by Lysosomal Disease Network Investigators

J.R. Utz, T. Crutcher, J. Schneider, P. Sorgen, C.B. Whitley, Biomarkers of central nervous system inflammation in infantile and juvenile gangliosidoses. Mol Genet Metab 114(2) (2015) 274-280. PMID: 25557439 [PubMedCentral - in process].

B.D. Yund, K.D. Rudser, A. Ahmed, V. Kovac, I. Nestrasil, J. Raiman, E. Mamak, P. Harmatz, R. Steiner, H. Lau, P. Vekaria, J.R. Wozniak, K.O. Lim, K. Delaney, C.B. Whitley, E.G. Shapiro, Cognitive, medical, and neuroimaging characteristics of attenuated mucopolysaccharidosis type II. Mol Genet Metab 114(2) (2015) 170-177. PMID: 25541100 [PubMedCentral - in process].

R.K. Rumsey, K.D. Rudser, K. Delaney, M. Potegal, C.B. Whitley, E.G. Shapiro, Acquired autistic behaviors in children with mucopolysaccharidosis type IIIA. J Pediatr 164(5) (2014) 1147-1151.e1. PMCID: PMC4041612.

D.A. Stevenson, K.D. Rudser, A. Kunin-Batson, E.B. Fung, D. Viskochil, E.G. Shapiro, P.J. Orchard, C.B. Whitley, L.E. Polgreen, Biomarkers of bone remodeling in children with mucopolysaccharidosis types I, II, and VI. J Pediatr Rehabil Med 7(2) (2014) 159-165. PMID: 25096868.

L.E. Polgreen, W. Thomas, P.J. Orchard, C.B. Whitley, B.S. Miller, Effect of recombinant human growth hormone on changes in height, bone mineral density, and body composition over 1-2 years in children with Hurler or Hunter syndrome. Mol Genet Metab 111(2) (2014) 101-106. PMCID: PMC4018305. Article freely available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4018305/

N.E. Taylor, D.R. Dengel, T.C. Lund, K.D. Rudser, P.J. Orchard, J. Steinberger, C.B. Whitley, L.E. Polgreen, Isokinetic muscle strength differences in patients with mucopolysaccharidosis I, II, and VI. J Pediatr Rehabil Med 7(4) (2014) 353-360. PMID: 25547887

A. Ahmed, C.B. Whitley, R. Cooksley, K.D. Rudser, S. Cagle, N. Ali, K. Delaney, B.D. Yund, E.G. Shapiro, Neurocognitive and neuropsychiatric phenotypes associated with the mutation L238Q of the α-L-iduronidase gene in Hurler-Scheie syndrome. Mol Genet Metab 111(2) (2014) 123-127. PMCID: PMC3939822. Article freely available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3939822/

R. Schiffmann, J. Mayfield, C. Swift, I. Nestrasil, Quantitative neuroimaging in mucolipidosis type IV. Mol Genet Metab 111(2) (2014) 147-51. PMCID: PMC4097300. Article freely available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4097300/

Related, Non-LDN-Funded Publications:

D. Gilden, R. Schiffmann, Leukoencephalopathy: "Before concluding treatment efficacy…". Neurology 84(3) (2015) 218-219. PMID: 25527269.

R. Schiffmann, The consequences of genetic and pharmacologic reduction in sphingolipid synthesis. J Inherit Metab Dis 38(1) (2015) 77-84. PMID: 25164785.

D.A. Wolf, S. Banerjee, P.B. Hackett, C.B. Whitley, R.S. McIvor, W.C. Low, Gene therapy for neurologic manifestations of mucopolysaccharidoses. Expert Opin Drug Deliv 12(2) (2015) 283-296. PMID: 25510418 [PubMedCentral - in process].

P.S. Kishnani, A.A. Beckemeyer, New therapeutic approaches for Pompe disease: enzyme replacement therapy and beyond. Pediatr Endocrinol Rev 12 Suppl 1 (2014) 114-124. PMID: 25345093.

P.S. Kishnani, S.L. Austin, J.E. Abdenur, P. Arn, D.S. Bali, A. Boney, W.K. Chung, A.I. Dagli, D. Dale, D. Koeberl, M.J. Somers, S.B. Wechsler, D.A. Weinstein, J.I. Wolfsdorf, M.S. Watson, Diagnosis and management of glycogen storage disease type I: a practice guideline of the American College of Medical Genetics and Genomics. Genet Med 16(11) (2014) e1. PMID: 25356975.

L. Ou, T.L. Herzog, C.M. Wilmot, C.B. Whitley, Standardization of α-L-iduronidase enzyme assay with Michaelis-Menten kinetics. Mol Genet Metab 111(2) (2014) 113-115. PMCID: PMC4014300. Article freely available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4014300/

Sanfilippo Syndrome Type B Clinical Trial of ERT Now Underway

(Continued from Page 4)

a Phase 1/2 study. SBC-103 was granted orphan designation by the FDA in April 2013 and the European Medicines Agency (EMA) in June 2013, and received *Fast Track* designation by the FDA in January 2015. Fast Track is an FDA process designed to facilitate development and expedite review of drugs to treat serious and life-threatening conditions, and to fill an unmet medical need to get important new drugs to patients as quickly as safely possible.

Chester B. Whitley, Ph.D., M.D., Professor, Advanced Therapies Program, Departments of Pediatrics and of Experimental and Clinical Pharmacology at the University of Minnesota, principal investigator of the Lysosomal Disease Network and investigator in this trial, said "Administering the very first dose of this recombinant enzyme is an important milestone for patients afflicted with this otherwise untreatable, lethal disease. This approach challenges the century-long dogma that the blood-brain barrier is impenetrable. The potential impact for these children cannot be overestimated. Sanfilippo syndrome was discovered at the University of Minnesota, and our team is uniquely prepared and excited to help assess treatment for these patients."

"The start of dosing in patients with Synageva's second, first-mover program and the first clinical trial of an enzyme replacement therapy for MPS IIIB is an important step forward for this community and the company," said Sanj K. Patel, President and Chief Executive Officer of Synageva. "The advancement of this program to clinical trials was made possible through the dedication and commitment from patients and their families affected by MPS IIIB, and the diligent efforts by our research and development team. Lysosomal disease enzyme replacement therapies with the recombinant form of the natural human enzymes are the gold standard of treatment for patients with these devastating diseases, and the results from this clinical trial will help further our understanding of the role of SBC-103 in MPS IIIB."

Synageva is also conducting natural history studies in MPS IIIB. These include a retrospective natural history study of deceased MPS IIIB patients that began in July 2013, and a prospective, longitudinal natural history study in living MPS IIIB patients that began in September 2014. Natural history studies can help build an understanding of the manifestations and progression of disease, and provide insights into biomarkers and other clinical indicators that may prove useful in establishing treatment outcome measures.

The source of this article's information is Synageva BioPharma Corp. Read the press release in its entirety at: http://ir.synageva.com/releasedetail.cfm?ReleaseID=892780

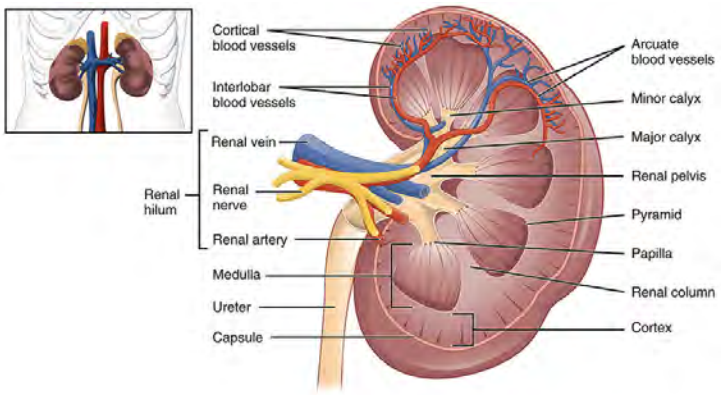
Bright Ideas

There is a 6-minute video about cystinosis and its effects upon the eyes: "Living With Cystinosis: A Closer Look" is on the Sigma-Tau Pharmaceuticals, Inc. Web site at: http://www.cystaran.com/patient_resources.php.

From McGraw Hill Publishers, there is a brief, clear animated explanation of how lysosomes arise and what they normally do. Visit: http://highered.mheducation.com/olc/dl/120067/bio01.swf

There is a broadly written overview of the lysosomal diseases at: http://emedicine.medscape.com/article/1182830-overview

There is a ~3-minute video entitled "Know Cystinosis Whiteboard Animation" which presents basic to intermediate-level cystinosis medical information at: http://vimeo.com/100519074. This video was posted by Raptor Pharmaceuticals Inc.



Kidney image is licensed under the Creative Commons Attribution 3.0 Unported license. Illustration originally from "Gross Anatomy of the Kidney," *Connexions* Web site. Visit: http://cnx.org/content/m46429/latest/?collection=col11496/1.6

Calendar of Upcoming Events

Rare Disease Day 2015 is February 28th. For a global overview, visit: http://www.rarediseaseday.org/. The NIH will celebrate the 8th annual Rare Disease Day on Friday, February 27th with a free and open-to-the-public all-day celebration and recognition of the various rare diseases research activities supported by NCATS' Office of Rare Diseases Research, the NIH Clinical Center, other NIH Institutes and Centers; the Food and Drug Administration's Office of Orphan Product Development; other federal government agencies; the National Organization for Rare Disorders; the Genetic Alliance; Global Genes; and Uplifting Athletes. Rare Disease Day at NIH will be held in the Masur Auditorium (Building 10) from 8:30 a.m. to 5:00 p.m. In addition to the various scheduled talks, there will be NIH Clinical Center tours, posters, and exhibits from many groups relevant to the rare diseases research community.

2015 American College of Medical Genetics and Genomics Annual Clinical Genetics Meeting, March 24 - 28, 2015 at the Salt Palace Convention Center, and the Salt Lake Marriott Downtown at City Creek, and the Hilton Salt Lake Downtown Hotel in Salt Lake City, Utah. Exhibit dates: March 25 - 27, 2015. Visit: http://ww4.aievolution.com/acm1501/

Cystinosis Research Foundation's Sixth Annual Day of Hope Cystinosis Family Conference, April 16 - 18, 2015 at Balboa Bay Resort, 1221 West Coast Highway, Newport Beach, CA 92663. Call Gina for reservations at (949) 630-4211. Visit: http://www.cystinosisresearch.org/day-hope-2015-crf-family-conference/

National Tay-Sachs and Allied Diseases 37th Annual Family Conference, April 16 - 19, 2015 at Hyatt Regency Reston, 1800 Presidents Street, Reston, Virginia. Visit: http://www.ntsad.org/index.php/event-listings/family-conference/2015-conference

American Society of Gene & Cell Therapy 18th Annual Meeting, May 13 - 16, 2015, in New Orleans, Louisiana. Visit the ASGCT homepage: http://www.asgct.org/

The Calliope Joy Foundation's *An Evening with Jim & Jill Kelly for Hunter's Hope* to benefit a National Care Network for Leukodystrophies, Friday, May 15, 2015 at the Rittenhouse Hotel, Philadelphia, PA. VIP Reception starts 6:00 p.m.; Dinner 7:00 - 10:00 p.m. Event Chair, Maria Kefalas: mkefalas67@gmail .com. Visit: http://www.thecalliopejoyfoundation.org/

The annual "Michael, Marcia & Christa Parseghian Scientific Conference" for Niemann-Pick type C disease research will be held June 11 -13, 2015 at the University of Notre Dame. Researchers will gather for three days to discuss the advances in NP-C research. This yearly meeting helps to form collaborations and determine the future direction of NP-C research. Visit: http://www.parseghian.org/events.html or call: (520) 577-5106.

Batten Disease Support and Research Association Family Conference 2015, July 9 - 12, 2015 at The Eaglewood Resort and Spa, 1401 Nordic Road, Itasca, Illinois. Visit: www.eaglewoodresort .com, and http://bdsra.org/

United Leukodystrophy Foundation's 2015 Annual Scientific Meeting and Family Conference, July 15 - 18, 2015 at Embassy Suites Downtown Old Market in Omaha, Nebraska. Visit: http://ulf.org/conferences

Cystinosis Research Network 2015 Family Conference, July 16 - 18, 2015 at Doubletree by Hilton Chicago Magnificent Mile, Chicago, IL. Visit: https://cystinosis.org/news/announcements/188-2015-family-conference-announced

Glycoproteinoses: Fourth International Conference on Advances in Pathogenesis and Therapy (a combined scientific and family conference), July 23 - 26th, 2015, in St. Louis, Missouri, USA. Visit: www.ISMRD.org

The Association for Glycogen Storage Disease 2015 Family/Professional Conference, September 18 - 19, 2015 in Oklahoma City, OK. For updates, visit: http://www.agsdus .org/

The Cystinosis Research Foundation presents a 6-minute video about cystinosis that provides some current updates about the status of research for treatments and cure: https://www.youtube.com/watch?v=u5mA8D69G-o

Indications™

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Keys to Understanding the Lysosomal Disease Network

Lysosomal Disease Network