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 . . .

FSIG was started in 1996 as a “kitchen table” support group formed by two Fabry patients and a supportive family member. Their aim was to share their particular understanding of this disease, combined with experience at gathering information and working with doctors, in order to benefit others. Since then, FSIG has been a continually growing and expanding organization constantly looking for new opportunities to assist in improving patient's lives. FSIG is led by its Executive Director Jack Johnson, one of the original co-founders.

FSIG pursues many avenues to assist those in the Fabry community. Primary among these are spreading infor-

The Lysosomal Disease Network (U54NS065768) is a part of the National Institutes of Health (NIH) Rare Diseases Clinical Research Network (RDCRN), supported through collaboration between the NIH Office of Rare Diseases Research (ORDR) at the National Center for Advancing Translational Science (NCATS), 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.

(Continued on Page 3)
What are the Lysosomal Disease Network’s Current Research Studies?

(Continued from Page 1)

LDN Protocol # 6720: Carotid structure and function in MPS syndromes: a multicenter study of the Lysosomal Disease Network
Principal Investigators: Aaron S. Kelly, Ph.D., and Raymond Wang, M.D.

LDN Protocol # 6721: Intravenous N-acetylcysteine for the treatment of Gaucher’s disease and Parkinson’s disease
Principal Investigators: Paul Tuite, M.D., and James Cloyd, PharmD.

Longitudinal research studies during this funding cycle have included:

LDN Protocol # 6702: Natural history and structural functional relationships in Fabry renal disease
Principal Investigator: Michael Mauer, M.D.

LDN Protocol # 6703: Longitudinal studies of brain structure and function in MPS disorders
Principal Investigator: Elsa G. Shapiro, Ph.D.

LDN Protocol # 6704: The natural history of mucolipidosis type IV
Principal Investigator: Raphael Schiffmann, M.D.

Principal Investigator: Lynda Polgreen, M.D., M.S.

LDN Protocol # 6706: A historical chart review and longitudinal follow-up of identified patients with Wolman disease or cholesteryl ester storage disease, lysosomal acid lipase deficiency
Principal Investigator: Gregory A. Grabowski, M.D.

LDN Protocol # 6709: Determination of cross-reactive immunological material (CRIM) status and longitudinal follow-up of individuals with Pompe disease
Principal Investigator: Priya S. Kishnani, M.D.

LDN Protocol # 6712: Longitudinal studies of the glycoproteinoses
Principal Investigator: Sara Cathey, M.D.

(Continued on Page 3)
What are the Lysosomal Disease Network’s Current Research Studies?

(Continued from Page 2)

LDN Protocol # 6714: A study of intrathecal enzyme replacement for cognitive decline in mucopolysaccharidosis I
Principal Investigator: Patricia I. Dickson, M.D., and Agnes H. Chen, M.D.

LDN Protocol # 6715: Longitudinal study of cognition with Niemann-Pick disease, type C
Principal Investigator: Marc C. Patterson, M.D.

LDN Protocol # 6716: Genotype-phenotype correlations of late infantile neuronal ceroid lipofuscinosis
Principal Investigator: Douglas Ballon, M.D.

LDN Protocol # 6717: Clinical and neuropsychological investigations in Batten disease
Principal Investigator: Jonathan Mink, M.D.

Meet Our Patient Advocacy Groups

(Continued from Page 1)

To facilitate these vital programs, FSIG maintains a confidential database of Fabry disease patients. This database also serves as a means of documenting the increasing numbers of diagnosed Fabry cases. There is no cost to join FSIG or to participate in its various support programs. FSIG relies on charitable contributions, in-kind donations, and corporate/industry donations and grants to continue providing services to those affected by Fabry disease.

FSIG has a team of medical advisors who contribute invaluable guidance and information. The medical advisors include Christine Eng, M.D., Associate Professor, Department of Molecular and Human Genetics at Baylor College of Medicine in Houston, TX; Edwin Kolodny, M.D., Professor of Neurology at New York University School of Medicine, New York City, NY; and William R. Wilcox, M.D., Ph.D., Professor of Human Genetics at Emory University, Atlanta, GA. (Dr. Wilcox has also been the principal investigator of a Lysosomal Disease Network pilot study, protocol number 6708 entitled “Pulmonary disease and exercise tolerance in boys with Fabry disease.”)

Meet Our Patient Advocacy Groups

(Continued from Page 1)

mation and increasing awareness of Fabry disease and its impact on the lives of those it touches. FSIG’s advocacy efforts include the medical community, pharmaceutical industry, and reimbursement, to name a few. FSIG has developed various patient-centered assistance programs to provide vitally-needed support specific for this unique community.

Additionally, FSIG’s community networking provides patients and family members or caregivers the ability to connect in a confidential manner to mutually support and encourage one another in an effort to alleviate some of the disease burden associated with Fabry disease.

The FSIG Expert Fabry Conference will be held Friday, February 14th through Sunday, February 16th at the Embassy Suites San Diego Bay hotel. This is especially convenient for attendees who also attend the Lysosomal Disease Network’s 10th annual WORLD Symposium in San Diego. The registration deadline for the FSIG Expert Fabry Conference was January 10, 2014, and the conference sold-out completely well before the deadline arrived. This shows the high esteem and appreciation in which the Fabry disease community holds FSIG, as well as their unmet need for in-depth information and interpersonal connections. Like membership in FSIG, the conference is free to Fabry patients and their immediate families or caregivers, including lodging, meals and conference registration.

Regarding the early ‘sold-out’ status of the FSIG Expert Fabry Conference, Mr. Johnson said: “I greatly underestimated the level of interest in attending this conference and chose a hotel that didn’t have facilities large enough to accommodate the degree of expansion needed to allow everyone interested to attend . . . We have already had to turn a number of people away, which has been agonizing, and have a waiting list if any

(Continued on Page 6)
In patients who have Fabry disease, end-stage renal disease (ESRD) occurs in more than 50% of males and up to 15% of females (1). The goals of enzyme replacement therapy (ERT) are to reduce suffering and prevent serious end-organ injury that can result in ESRD, stroke, or serious heart disease (1-4). ERT has been approved for Fabry disease patients based on clearance within 5 months of globotriaosylceramide (GL-3) from glomerular and peritubular capillary (PTC) endothelial cells and glomerular mesangial cells (5). Nevertheless, clearance from arterial smooth-muscle cells (ASMC), distal tubular cells (DTC), and especially, podocytes (PC) was incomplete even after 11 months of ERT (5). While DTC had cleared by 5 years (6), there was only a modest reduction of GL-3 in PC in 4 of 6 patients, while 2 did not improve and, in no case did PC clear completely.

Dr. Michael Mauer of the University of Minnesota in Minneapolis leads LDN-supported study protocol number 6702 that seeks to: 1) evaluate GL-3 accumulation per PC, and PC number per glomerulus, as a function of age in ERT-naïve male and female children and adults with Fabry disease; 2) evaluate the effects of age at ERT initiation, gender, and duration and dose of ERT on PC and other renal cell GL-3 clearance in children and adults with Fabry disease; 3) evaluate the effects of age at ERT initiation, gender, and duration and dose of ERT on PC foot process width in children and adults with Fabry disease; 3) evaluate the effects of age at ERT initiation on PC number in males with Fabry disease.

Importantly, Dr. Mauer’s morphometric electron microscopic (EM) measurements of the fraction of the volume of PC cytoplasm occupied by GL-3 inclusions [Vv(Inc/PC)] increased with increasing age, and correlated with proteinuria in ERT-naïve children with Fabry disease (7). This was not the case with glomerular endothelial or mesangial cells (7). Since risk of Fabry renal disease increases with age (1), and proteinuria is a strong predictor of glomerular filtration rate loss in ERT-naïve (9) and ERT-treated (10) adult male Fabry disease patients, his team’s finding of progression of glomeruli Fabry lesions only in PC is a highly significant indicator of an important role for PC in the development of clinically serious Fabry nephropathy.

Increased foot process width (FPW), an important indicator of PC injury, also increased with increasing age in Fabry disease children, and FPW correlated strongly and directly with urinary protein excretion (7). Initiation of ERT after overt proteinuria is present has not reduced proteinuria (8). These findings raise serious concern that once heavy proteinuria is present in Fabry disease males, ERT is not fully effective in reducing progression to ESRD. Thus, it is highly plausible that proteinuria in male Fabry disease patients is associated with increasing PC GL-3, and that ERT as currently dosed cannot fully clear PC GL-3.

Recently, using a subjective scoring system, PC GL-3 clearance after 5 years ERT in young Fabry patients was also found to be incomplete, and was found to be ERT dose-dependent (11). Importantly, there was a direct relationship between PC GL-3 clearance and reduction in proteinuria in this study. It is likely that once PC damage and loss are sufficiently advanced, new disease-progression promoters emerge which are unresponsive to ERT. Perhaps this “point-of-no-return” is related to the relative inability of PC to replicate (12) and the complex structural relationship of PC with their adjacent PC (13). Thus focal and global glomerulosclerosis and their downstream consequences of interstitial fibrosis and tubular atrophy are major late components of Fabry nephropathy progression toward ESRD (14).

In protocol 6702, Dr. Mauer’s team seeks to answer the following seven hypotheses: 1) GL-3 inclusions per PC will be consistent with increasing PC GL-3 content with increasing age; 2) the rate of PC GL-3 accumulation in affected PC in females will be similar to that of PC in males; 3) PC number per glomerulus decreases with age and correlates inversely with PC GL-3 content; 4) ERT started at younger ages, given at higher doses and for longer duration will be more effective in reducing PC, DTC and ASMC GL-3 in Fabry disease patients; 5) GL-3 reduction in males and in affected cells in females.
will be similar; 6) ERT started at younger ages and given at higher doses and for longer duration will be associated with greater normalization of increased FPW; and 7) ERT started at younger ages will be associated with lower rates of PC loss. Lysosomal Disease Network protocol number 6702 is also supported by Genzyme/Sanofi.

References:


Publications Arising From This Protocol:


(Continued from Page 4)
Meet Our Patient Advocacy Groups

(Continued from Page 3)

space becomes available due to registered participants canceling. For our next meeting we will be sure to be prepared for greater expansion should it be needed."

The FSIG Expert Fabry Conference is recognizing excellence by awarding two prizes: the Best Doctor or Medical Professional Award, and the Best Caregiver Award. Nominations were made on the FSIG Web site by Fabry disease patients, family and caregivers. If you are a Fabry disease patient, family member or caregiver who missed the opportunity to attend this conference due to not being aware of it, be sure to join FSIG so that you will be informed about future conferences. To join FSIG, go to: http://www.fabry.org/FSIG.nsf/Pages/JoinFSIG.

Check Your Knowledge of Lysosomal Diseases

How well do you know Fabry disease?

By Evelyn S. Redtree, M.S. and Brenda Diethelm-Okita, M.P.A.

Fabry disease, or α-galactosidase-A deficiency, is also sometimes called Anderson-Fabry disease; angiokeratoma corporis diffusum; angiokeratoma diffuse; ceramide trihexosidase deficiency; GLA deficiency; glycolipid lipidosis; or hereditary dystopic lipidosis. In Fabry disease, α-galactosidase-A (α-GAL A) deficiency results in accumulation of the ganglioside globotriaosylceramide (also known as GL-3 or Gb3) within lysosomes. Globotriaosylceramide accumulation occurs in cells all over the body, but most preferentially in the walls of blood vessels. As this lipid compound accumulates over time, the lumina of the blood vessels become narrowed, leading to decreased blood flow with resulting inadequate tissue nourishment. Although this process occurs in all blood vessels throughout the body, it particularly affects small blood vessels in the skin, kidneys, cardiovascular system and autonomic nervous system.

Genetic basis of Fabry disease

Fabry disease inheritance is X-linked dominant with incomplete penetrance in heterozygous females. The responsible defective GLA gene has been identified at location Xq21.33-q222. More than 600 Fabry disease-causing mutations in the GLA gene have been identified so far. Depending upon the mutation(s) involved, the range and severity of symptoms varies among patients. No Fabry disease patient will necessarily present with all of the possible disease symptoms at any one time, or at any specific age. When the defective gene is carried on a mother’s X chromosome, her sons have a 50 percent chance of inheriting the disorder, and her daughters have a 50 percent chance of being a carrier. When the defective gene is carried on a father’s X chromosome, his daughters are ‘obligate carriers’, since they inherit an X chromosome from each parent. Although a milder form of Fabry disease is most common in females, some affected females have manifestations as severe as males with Fabry disease.

Diagnosing Fabry disease

When Fabry disease is suspected—either on the basis of clinical signs and symptoms, or by the diagnosis of a relative with Fabry disease—diagnosis in affected males can be confirmed by a simple blood test measuring the activity of α-GAL A enzyme.

In contrast, the enzymatic identification of carrier females is less reliable due to the random X-chromosome inactivation in carriers. Obligate carriers (daughters of classically-affected males) may have α-GAL A enzyme activity ranging from normal to very low. Thus, in females, only the identification of an α-GAL A mutation in the GLA gene provides completely accurate carrier identification. It is important to determine the mutation status in all at-risk females in families with Fabry disease, including those who are currently asymptomatic.

Subtypes of Fabry disease and their presentation

Complete absence of, or less than 1% of normal levels of, α-GAL A enzyme results in the “classic” subtype of Fabry disease. Classic Fabry disease typically has an early onset, which can occur in childhood or adolescence. Commonly, the earliest signs and symptoms of classic Fabry disease can include:

(Continued on Page 7)
Check Your Knowledge of Lysosomal Diseases

How well do you know Fabry disease?

(Continued from Page 6)

- Episodic excruciating pain and burning sensations in the hands and feet which are often provoked by physical exercise, fatigue, fever, stress, heat exposure, or change in weather conditions; such episodes are called Fabry’s crises, and may persist for hours or days; pain may also be present in the arms or legs;
- Sharp pain which can occur anywhere in the body;
- Gastrointestinal problems, including abdominal pain and cramping, diarrhea, bloating, nausea, and inability to gain weight;
- Raised or flat, dark-red, purplish or blue-black benign skin papules (angiokeratomas), the majority of which occur between the umbilicus and the knees;
- Inability to perspire adequately or to perspire at all (anhydrosis), which results in overheating during physical activity, with resulting discomfort and fevers;
- Corneal clouding (corneal dystrophy) that does not affect vision; and
- Delayed puberty or delayed growth.

Affected individuals whose α-GAL A enzyme is present at greater than 1% of normal levels have the more-or-less attenuated, later-onset subtype of Fabry disease. They usually do not experience the classic-subtype early symptoms listed above. Rather, symptoms of kidney, heart or cerebrovascular involvement usually occur between the ages of 30 to 45. It is the first appearance of such kidney, heart or cerebrovascular symptoms that often leads to the initial diagnosis of late-onset Fabry disease. Males and affected females with late-onset Fabry disease may experience any of the following symptoms or complications. Individuals with the classic-subtype of Fabry disease, as they age, may also add any of the following symptoms or complications to their early symptoms noted above:

- Severe kidney problems resulting in renal insufficiency and ultimately, end-stage renal failure;
- Myocardial ischemia and infarction;
- Transient ischemic attacks;

(Continued on Page 8)

Meet the Principal Investigators

Michael Mauer, M.D. is the Principal Investigator of the Lysosomal Disease Network protocol number 6702 entitled “Natural history and structural functional relationships in Fabry renal disease” (see pages 4-5). Dr. Mauer is Co-Director and Professor, Division of Nephrology, Department of Pediatrics, at the University of Minnesota in the Twin Cities.

For more than thirty years Dr. Mauer has been studying renal biopsies to gain insights into structural-functional relationships in slowly progressive renal diseases, and to use biopsies as primary endpoints in clinical trials. This work initially concentrated on diabetic nephropathy (DN), the leading cause of kidney failure in the Western world. Dr. Mauer directed a large clinical trial aimed at primary prevention of DN. He is co-principal investigator of an NIH-funded early-treatment trial in early renal function loss in DN. Dr. Mauer is studying the cellular, molecular and genetic basis of DN. His goal is to help unravel the relationships of kidney structural changes to kidney functional changes in DN. He is also evaluating the reversibility of DN injury following cure of diabetes with pancreas transplantation, and recurrence of DN in diabetic kidney transplant recipients. This research is supported by the NIH, the Juvenile Diabetes Foundation International, and Merck Pharmaceutical Company.

In the past decade, Dr. Mauer’s research has also included Fabry disease studies. His work in Lysosomal Disease Network protocol number 6702 is also supported by Genzyme/Sanofi. Dr. Mauer has collected the largest set of Fabry disease research kidney biopsies in treatment-naïve patients, and he is currently collecting
Meet the Principal Investigators

(Continued from Page 7)

post-treatment biopsies. He also serves as a consultant to Genzyme/Sanofi in the design and conduct of clinical trials; and to Amicus in the performance and interpretation of renal biopsy studies in Fabry disease.

Dr. Mauer is the Chair of the North American Fabry Registry Advisory Board. In 2009, Dr. Mauer was inducted into the Academy for Excellence in Health Research of the University of Minnesota Academic Health Center. From 2000 to 2012, he was Director, Pediatric Solid Organ Transplant Program at Amplatz Children’s Hospital at the University of Minnesota. View Dr. Mauer's Amplatz Children’s Hospital interactive Web page at: http://www.uofmchildrenshospital.org/Providers/Bio/D_122025.

Selected Publications:


LDN Research Matters

(Continued from Page 5)


Check Your Knowledge of Lysosomal Diseases

How well do you know Fabry disease?

(Continued from Page 7)

- Stroke;
- Cardiac arrhythmia;
- Hypertension;
- Cardiomegaly;
- Left ventricular hypertrophy;
- Hypertrophic cardiomyopathy;
- Cardiac failure;
- Mitral valve prolapse or insufficiency;
- Lymphedema in the feet and legs;
- Hearing loss which can be progressive, and possible sudden deafness;
- Frequent bowel movements after eating;
- Joint or back pain;
- Tinnitus and/or vertigo;
- Headache;
- Generalized weakness;
- Nausea and/or vomiting;
- Chronic bronchitis or shortness of breath.

As implied by these complications, patients with Fabry disease often die prematurely of complications from strokes, heart disease, or renal failure.

Misdiagnosis of Fabry disease

Misdiagnosis is common in Fabry disease due to its rarity. Fabry has been mistaken for:

- Ménière’s disease
- Crohn’s disease
- Multiple sclerosis
- Rheumatic fever
- Arthritis
- Raynaud syndrome
- Irritable bowel syndrome
- Erythromelalgia

Incidence of Fabry disease

Fabry disease occurs amongst all races and ethnicities. The “classical” subtype of Fabry disease, characterized

(Continued on Page 9)
Check Your Knowledge of Lysosomal Diseases

How well do you know Fabry disease?

(Continued from Page 8)

by early onset, affects approximately 1:40,000 men. The later-onset subtype is more frequent, affecting about 1:1,500 to 1:4,000 males, depending upon the demographics of the population under study.

Fabry disease treatments

In March 2001 agalsidase beta and agalsidase alfa were each approved in Europe for enzyme replacement therapy (ERT) treatment of Fabry disease (they are also used in scores of non-European countries). In April 2003 agalsidase beta was approved by the U.S. Food and Drug Administration for ERT treatment of Fabry disease. These enzyme-replacements are a form of the human enzyme produced by recombinant DNA technology, administered intravenously on a recurring frequent schedule. Enzyme replacement therapy is not a cure for Fabry disease, but can allow improved metabolism and partially prevent disease progression. It has been found to reduce pain, reduce lipid accumulation, improve cardiac function, stabilize renal function, and improve patients’ reported quality of life. The pain occurring in Fabry disease may also need to be managed with analgesics, anticonvulsants, and/or non-steroidal anti-inflammatory drugs. Gastrointestinal hyperactivity may need to be treated with metoclopramide. Some ERT-treated individuals may still require dialysis or kidney transplantation.

Fabry disease clinical trials in progress

By visiting http://clinicaltrials.gov/ct2/search/index and using the search term Fabry disease, about 87 clinical studies researching the natural history or treatment of Fabry disease can be viewed. For example, included are four ongoing clinical drug trials that are being conducted by Amicus Therapeutics, Inc. All are now closed to recruitment. They are:

Phase 3 global clinical study, named the FACETS Study (FAB-AT1001-011), to assess the safety and efficacy of orally-administered migalastat hydrochloride (migalastat HCl) (also known as AT1001) in treatment-naïve individuals with Fabry disease. This is a placebo-controlled, double-blind Phase 3 study. Patient recruitment for this study was closed on October 19, 2011. ClinicalTrials.gov study number: NCT00925301

Phase 3 global clinical study, named the ATTRACT Study (FAB-AT1001-012). This is a randomized, open-label, 18-month Phase 3 study investigating the safety and efficacy of orally-administered migalastat HCl for Fabry disease compared to current standard-of-care ERT using agalsidase beta or agalsidase alfa, in individuals who currently are receiving ERT. Patient recruitment for this study was closed on October 22, 2012. ClinicalTrials.gov study number: NCT01218659

Phase 2 extension study 205 (FAB-CL-205) is a Phase 2A migalastat HCl co-administration monotherapy clinical trial designed to evaluate the safety and effects of migalastat HCl on agalsidase ERT, when migalastat HCl is orally administered to individuals with Fabry disease prior to the agalsidase ERT infusion. This is an open-label long-term safety and tolerability study of AT1001 in patients with Fabry disease who have completed a previous Phase 2 AT1001 study. ClinicalTrials.gov study number: NCT00526071

Phase 2 Study 013 (AT1001-013) is an open-label Phase 2 study to compare a single administration of oral migalastat HCl co-administered with infused ERT (agalsidase beta or agalsidase alfa) versus ERT alone. Each patient receives their current dose and regimen of ERT alone at one infusion, and receives oral migalastat HCl (150 mg or 450 mg) administered prior to ERT at their next infusion. ClinicalTrials.gov study number: NCT01196871

Clearly, the search for an effective oral medication is an important focus of current Fabry disease pharmacological research. Today’s Fabry disease patients are fortunate to live in a time of such innovative diagnosis and treatment, with the possibility of ever-improving therapy on the horizon.


(Continued on Page 10)
Check Your Knowledge of Lysosomal Diseases

How well do you know Fabry disease?

(Continued from Page 9)

Learn More . . .

Online Mendelian Inheritance in Man – Fabry Disease http://omim.org/entry/301500

Overview of Fabry Disease in Wikipedia: http://en.wikipedia.org/wiki/Fabry_disease
Excellent photographs are found in this article.

A book presented in an online format by the National Center for Biotechnology Information, U.S. National Library of Medicine:
http://www.ncbi.nlm.nih.gov/books/NBK11586/ “Fabry Disease: Perspectives from 5 Years of the Fabry Outcome Survey” PMID: 21290683

Orphanet – Fabry disease http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=324

“Fabry Disease: Important Facts for Women” From: Emory University School of Medicine genetics.emory.edu/pdf/Fabry.pdf

Calendar of Upcoming Events

Lysosomal Disease Network’s 10th annual WORLD Symposium™, February 11 - 13, 2014 in San Diego, California, USA. For a link to the official meeting registration page, visit: http://www.LysosomalDiseaseNetwork.org/.


13th International Symposium on MPS & Related Diseases, August 13 - 17, 2014 in Costa do Sauipe, Bahia State, Brazil. For more information, visit: http://www.mps2014.com/new/.


American Society of Human Genetics 64th Annual Meeting, October 18 - 22, 2014 in San Diego, California, USA. For more information, visit: http://www.ashg.org/2014meeting/.


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