FALL 2022

INSIDE

FSIG Connection

News from the Fabry Support & Information Group

3 things every female Fabber needs to know

By Christy Flater
FSIG Contributor

During my childhood years, I was always under the assumption that Fabry disease would not be "my disease," because no one knew any different at that time. However, we do know better now.

As women are included in more studies and clinical trials, more findings have become available to confirm that Fabry is not only a male symptomatic disease. If you are a female diagnosed with Fabry, then most likely this doesn't come as a surprise to you. I always knew there was something different inside my body, but I would brush it aside or add it to the box of symptoms associated with my menstrual cycle.

FEMALES & FABRY

Women need to be given permission to claim our Fabry symptoms, so we can be empowered to work with them instead of working against them or ignoring them altogether. I wish I could go back to my younger self, give her a big hug and let her know that she is not alone. To tell her it's possible to live a fulfilling life without the constant struggle of the unknown. Knowledge truly is power. And for women, that power looks like the full disclosure of options for caring for our bodies with Fabry.

COURTESY OF CHRISTY FLATER

Christy Flater lives in Utah with her husband and three children. She runs the Hope Gifted Podcast and serves as an advocate for Fabry patients.

Men diagnosed with Fabry will share a similar story of their journey through the unknown until the official diagnosis. However, there is one distinct difference—when males get their diagnosis, the sentence ends with a period. It comes with immediate action, education about treatment and the regular assessments in how to care for his body.

A female diagnosis comes with a question mark. What symptoms will she have? How severe will they be? Is treatment the best way to

See FEMALE, Page 2

FSIG organizes Fabry Women's Summit

By Lisa Bacon
FSIG Programs Director

As part of its ongoing effort to raise awareness in Fabry females, FSIG created the first Fabry Women's Summit. The weekend retreat, which took place Nov. 11-13, brought females and caregivers together from across the United States.

This summit was designed to educate with knowledge and skills so we can stop living in the shadow of Fabry and aims to empower us to live better lives and make good health choices.

FSIG hosted the summit in the charming city of Charlotte, NC, at the Springhill Suites Uptown. This event also gave attendees the chance to get to know other Fabry women, learn sustainable daily wellness habits, restore and rejuvenate their body and address a need or problem in their life.

Registration opened on Sept. 1 and was completely full by Sept 15. The summit was sponsored by Amicus Therapeutics, Chiesi Global Rare Diseases, Sanofi, Freeline, and Sangamo Therapeutics.

WELCOME

Dear Friends,
Welcome to the last newsletter of the year! 2022 has been a whirlwind of activities. From the annual conference to patient meetings and the first-ever Women's Summit, the FSIG staff has been back to "business as usual."

This issue highlights Fabry in females. As progress has been made with recognizing females as symptomatic, there is still a long way to go with educating the greater medical community and Fabry families. Our goal is to support this progress with awareness, personal stories and continued pressure to include females in clinical trials.

As this year comes to an end, cherish every moment you have with your family and loved ones. Have a wonderful holiday season!

Jack

Jack Johnson, Executive Director

Study examines economic burden of RDs

By Pedro Andreu, PhD, et al
Chiesi Global Rare Diseases

Understanding the cost drivers and economic impact that a lack of available treatments poses for people living with rare diseases is critical for highlighting the unmet needs of the community and how those needs may be addressed.

Chiesi Global Rare Diseases, with support from IQVIA, set out to study the direct, indirect, and mortality-related costs for a sample of 24 rare diseases across five therapeutic areas to evaluate the burden of care when treatment is available versus when no treatment exists, and to compare these costs to common mass market diseases.

The resulting report provides a benchmark for cost disparities and assesses how the burden of rare diseases is impacted by treatment availability.

Key findings from the study: Rare diseases impose a substantial economic burden that is reduced by treatment availability.

- The burden of rare diseases is approximately 10x higher than mass market diseases on a per patient per year (PPPY) basis.
- A lack of treatment for a rare disease is associated with a 21.2% increase in total costs PPPY.
- The cost for 8.4 million patients in the U.S. impacted by 373 rare diseases considered in this analysis is estimated to be $2.2 trillion per year.
- Based on this estimate, the societal responsibility for all known rare diseases may be in the range of $7.2 trillion to $8.6 trillion per year.
- Investment in diagnostic tools, newborn screening, and development of new therapies is justified.
- Empirical studies need to consider many aspects of healthcare costs to gain a full picture of the overall burden of rare diseases. Access to therapies for people living with rare diseases generates significant value for society.

Rare diseases present a societal concern due to difficulties and delays in diagnosis, a lack of treatment availability, difficulty in developing new treatments and the need for favorable regulatory and access conditions. In the U.S., rare diseases are defined as those affecting fewer than 200,000 people.It is estimated that approx. 30 million people in the U.S., half of them children, are affected by more than 7,000 rare diseases.

Read more: bit.ly/burdeneval

FEMALE continued from page 1

go? How bad does "bad" need to be before she gets help?

It can be overwhelming to take on the diagnosis of this disease. But along my journey with Fabry, I've gained three key life lessons. They are not limited to females, but they are shared in the spirit of heartfelt encouragement to the sisterhood of women with Fabry.

1. Allow yourself to take a break.

When we wake up, we are already running on empty. So it's vital to give yourself pit stops throughout the day before you completely break down.

One of the most frustrating byproducts of living with Fabry disease is the difficulty of planning ahead. I feel the anxiety of my schedule when I see a day that is too full, and the uninvited thought that taunts me of whether my body will be able to handle it. I've learned that actively saying no to certain things can allow me to say a better yes to the things I value.

2. Advocate for your body, which will advocate for your future.

Fabry is progressive, which mean prevention is always the best policy. Advocating for yourself or others in your family is simply asking for support from another person to help you express your views and receive the type of care you deserve. Be willing to invest the time and have the courage to share your voice to receive the proper care for your body. You are looking for a care team that will listen to you.

You are prolonging your life when you speak up to find a medical team that will partner with you in this journey.

3. Include mental and emotional well-being when getting your regular assessments.

When you are handling a chronic disease, it's only a matter of time before anxiety and depression show up. It doesn't always happen at the beginning of the journey, and it can look different each time it appears. Finding positive outlets to help you handle stress and learn to cope will give you the ability to operate better in the day-to-day. Mental health is important at every stage of the journey, because it will give you the ability to make healthier choices and accurately relay your perception to others around you to get the best support available.

Khalil Gibran—a Lebanese-American writer, poet and visual artist—once said, "Out of suffering have emerged the strongest souls." Being diagnosed with Fabry is not for the faint of heart. Please know that I see you and the struggles you carry in silence. I understand the burden you feel of having to prove that Fabry affects your quality of life, even when the answers are not that apparent in the test results.

I hear you when you say you are doing more than people will ever realize in taking that next step forward. In the Fabry community, you do not need to prove anything, because we believe you.

I won't ever be thankful for Fabry disease, but I am grateful for the reflection of compassion, strength and love it has shown me through the beautiful faces of so many that are smiling through their struggles, too.

Mexico introduces Rare Diseases Diagnostic Unit

By Melissa James
FSIG Contributor

In Mexico, only 20 rare diseases are recognized—including Fabry Disease, Turner Syndrome, Pompe Disease, Hemophilia, Spina Bifida, Cystic Fibrosis, Histiocytosis, Congenital Hypothyroidism, Phenylketonuria, Galactosemia, Type 1, 2 and 3 Gaucher Disease, Congenital Adrenal Hyperplasia and Homocystinuria.

Because so few rare conditions are officially acknowledged, most do not have treatments. But on June 23, Mexico announced the creation of its new Rare Diseases Diagnostic Unit (UDER), part of the Faculty of Medicine of the National Autonomous University of Mexico (UNAM). The unit is located in the Conde de Valenciana Foundation Ophthalmology Institute. The hope is that this new facility will be a national reference center for genetic diagnosis—potentially improving the quality of life for patients.

"It is an unexplored field, which has not been given the focus it should have, and the only way we know so far to solve the problem, the dilemma of why, how and who they attack, is the application of new techniques. of molecular biology and molecular biochemistry. The creation of this Unit dedicated to these techniques is a success, and will contribute in an important way both to the dissemination and to the intimate collaboration that we have with the Faculty of Medicine," said Ana Maria Lopez Colome, member of the board of trustees of the Conde de Valenciana Foundation.

Rare disease foundation appeals to India leaders

By Melissa James
FSIG Contributor

In May, the Rare Diseases India Foundation appealed to the country's prime minister and health minister to guide certain healthcare facilities in immediately beginning treatment for patients with life-threatening rare disorders, such as Fabry.

"It has been over two months since the Ministry of Health issued an office memorandum extending the funding support of up to [5 million rupees, or $60,362USD] for all categories of rare diseases, but the treatment of these patients is yet to start at the designated Centres of Excellence (CoEs)," said RDIF director and co-founder Saurabh Singh in a statement. He went on to say:

"It seems that the CoEs are still awaiting clear-cut instructions from MoHFW (Ministry of Health and Family Welfare) to start treatment."

Singh described his deep concerns over the fatal risks faced by many young people, especially children, due to lack of immediate support for their treatment. In fact, it's estimated that at least four of these children have already lost their lives this year while awaiting treatment support, according to the statement.

As many as 340 patients have been deemed eligible by the eight designated CoEs after the necessary diagnostic tests and physical examination. Their diagnoses were mostly lysosomal storage disorders like Pompe disease, Gaucher disease, Fabry and MPS I.

Read more: bit.ly/treatrare

Fabry GLA gene variant found in Parkinson's patients

By Lindsey Shapiro, PhD
FabryDiseaseNews.com

(May 20, 2022) A variant in the GLA gene associated with Fabry disease was found in four women with Parkinson's disease, but they had no Fabry symptoms, according to results from a study of 236 Parkinson's patients.

According to the research team, the significance of the mutation and the relationship between the two diseases requires further investigation.

"The results of this study suggest a possible relationship between [Fabry] and [Parkinson's] in a small proportion of cases," the researchers wrote. "Nevertheless, the GLA variant found in our cohort is classified as a variant of unknown significance. Therefore, its pathogenic causative role in the context of [Parkinson's] needs further elucidation, and these findings should be interpreted with caution."

The study, "Prevalence of Fabry Disease among Patients with Parkinson's Disease," was published in the journal *Parkinson's Disease.*

Lysosome dysfunction also is thought to be important in Parkinson's disease, a neurodegenerative disease characterized by abnormal buildup of the alpha-synuclein protein. As such, there is an increasing interest in understanding the relationship between lysosomal storage diseases and Parkinson's.

A previous study reported an increased prevalence of Parkinson's among people with Fabry and their immediate relatives. Decreased alpha-GalA activity also has been reported in Parkinson's patients, suggesting a relationship between the two diseases.

To systematically evaluate the relationship, the research team examined the prevalence of Fabry among 236 Parkinson's patients recruited to a movement disorders center in Kosice, Slovakia. Among the 130 male patients, 20 (15%) had low alpha-GalA levels. Lyso-GB3 levels were normal in these 20 men.

Of note, only one mutated copy of GLA is necessary to have Fabry. Since the gene is on the X chromosome, of which females have two copies, a second, healthy copy may allow females with one mutant copy to have normal enzyme levels. For this reason, measuring alpha-GalA levels is not considered as clinically useful for diagnosis in women, and thus was not performed in this study.

Genetic testing of the 20 alpha-GalA deficient males and all 106 female patients revealed that four, all of whom were female, had the same mutation in the GLA gene (c.937G>T).

Among these four women, the age of Parkinson's onset was greater than 55 years. All four had typical motor symptoms of Parkinson's, and non-motor symptoms of urinary problems, sleep issues, and mood problems were each reported in three of the four women. Two had normal cognition and two had mild cognitive impairment.

Read full story: bit.ly/GLAgene

Sangamo gene therapy seems to work for Fabry

Press Release

(Aug. 22, 2022) Sangamo Therapeutics, a genomic medicine company, today announced updated preliminary results from the Phase 1/2 STAAR clinical study evaluating isaralgagene civaparvovec, or ST-920, a wholly owned gene therapy product candidate for the treatment of Fabry disease.

These latest data show that, as of the Feb. 14, 2022, cutoff date, the investigational treatment continued to be generally well tolerated, with no treatment-related adverse events above Grade 1 (mild). These updated data are available on Sangamo's website on the Events & Presentations page.

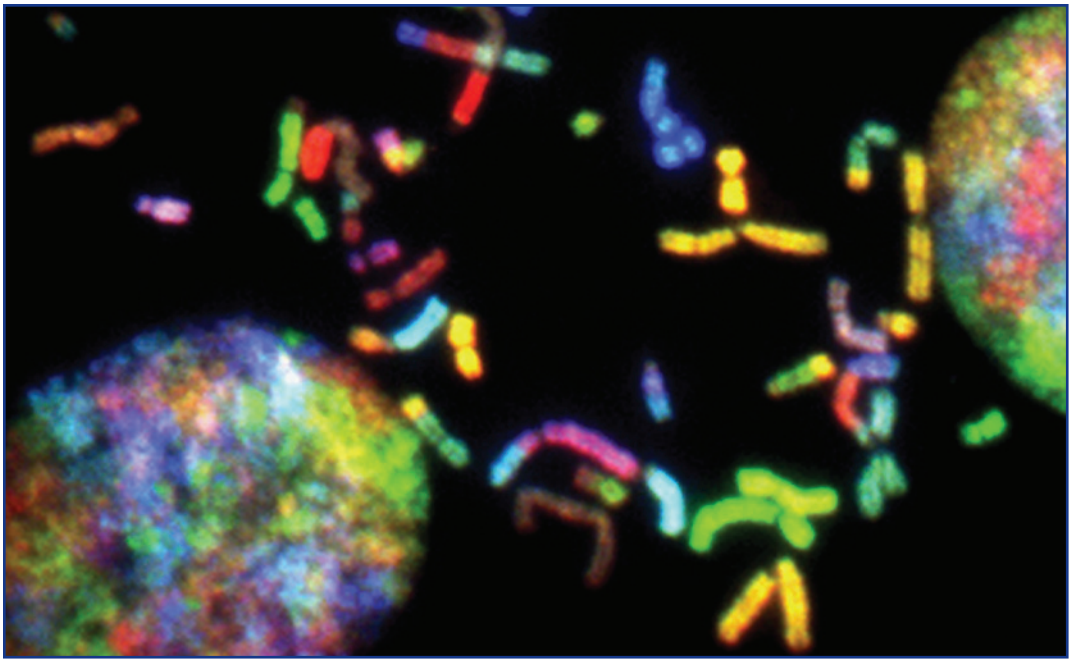
"These updated preliminary results continue to demonstrate the potential of isaralgagene civaparvovec gene therapy to safely address the most challenging symptoms of Fabry disease," said Jaya Ganesh, MD, Division of Medical Genetics and Genomic Sciences at the Icahn School of Medicine at Mount Sinai and investigator of the Phase 1/2 study. "I am excited to see whether these encouraging trends continue into the next dose cohort and beyond, as we progress this potential treatment for a very challenging illness."

KEY FINDINGS

- **ST-920 continued to be generally well tolerated across three dose cohorts in the six treated patients**
- **The five longest treated patients exhibited elevated α-Gal A activity, ranging from nearly 3-fold to nearly 17-fold above mean normal, up to 15 months as at the last date of measurement**
- **One patient was withdrawn from enzyme replacement therapy (ERT) and demonstrated significantly elevated levels of α-Gal A activity at 12 weeks post withdrawal**
- **Since the cutoff date, an additional five patients have been dosed and an additional four patients in the dose escalation phase have been withdrawn from ERT. The Phase 1/2 STAAR study has progressed into the dose expansion phase.**

Three patients have anecdotally reported improvements in their symptoms, including improvements in the ability to sweat, a primary and common Fabry disease symptom. No progression of Fabry cardiomyopathy was observed in those patients who presented with signs of cardiomyopathy on cardiac MRI at baseline.

Related coverage: bit.ly/sangamotherapy



New gene sequencing strategy could speed up Fabry diagnosis

By Marisa Wexler, MS
FabryDiseaseNews.com

(July 8, 2022) Mendelics and Takeda are partnering for a new program that aims to use a genetic sequencing strategy to make diagnosis of Fabry disease easier and faster.
Diagnosis of Fabry disease often is a lengthy and complicated process, in part because the disease can manifest very differently in different individuals.

According to Mendelics—a Brazilian company that specializes in a type of genetic analysis called next-generation sequencing, which can determine the exact sequence of genes—Fabry disease is under-diagnosed worldwide.

Because the GLA gene is on the sex-determining X chromosome (females have two while males have one), Fabry disease diagnosis often is especially challenging in women, who generally don't show the same severity of symptoms as males with the disease. Delays in getting the correct diagnosis lead to delays in initiating appropriate treatments—and delayed treatment is generally associated with poorer clinical outcomes.

Traditional workups for the diagnosis of Fabry disease usually start by doing biochemical analyses on samples of blood or urine, looking for reduced activity of the Gal A enzyme and abnormal increases in the fatty molecules that are associated with the disease. Then, if results indicate potential Fabry disease, the patient's DNA can be sent for genetic testing to confirm the diagnosis.

According to Mendelics, doing biochemical testing first requires waiting for results from the tests to be available from a laboratory, which often takes a while and tends to extend diagnostic delays. The company's novel diagnostic strategy, called Sequencing First, involves reversing the normal diagnostic flow: first doing genetic testing to look for potential disease-causing mutations in the GLA gene, then doing biochemical testing for confirmation of samples that are positive on genetic tests.

"Sequencing First is an innovative approach for the diagnosis of some rare genetic diseases, which consists of DNA sequence analysis as the first diagnostic approach, using biochemical or functional tests as complementary analysis, after an eligible genetic result," David Schlesinger, geneticist and CEO of Mendelics, said in a press release. "We reversed the order of exams so that the patient benefits from a faster and more accurate diagnosis."

The test is done on a sample collected by swabbing the inner cheek (buccal swab), and results are available in up to 30 days, which, according to Mendelics, is a much shorter waiting time compared to traditional approaches.

"The test performs the sequencing of all regions of the GLA gene with greater sensitivity, shorter logistics and execution time," Schlesinger said.

Read full story: bit.ly/sequencing1st

Study: Bone density lower in men than women with Fabry

By Steve Bryson, PhD
FabryDiseaseNews.com

(July 22, 2022) High levels of calciprotein particles (CPP) — tiny structures that transport excess minerals in the bloodstream—were found in adults with Fabry disease who have a low bone mineral density (BMD), a study revealed for the first time.

The hip bone and the top of the upper leg bone (femoral neck) were most affected.

In addition, elevated CPP was higher in men with Fabry than in women, a difference not seen in healthy individuals.

Further research is needed to understand the relevance of sex-related differences and determine whether CPP measurements may help assess bone disease in Fabry, the researchers noted.

The study, "Reduced hip bone mineral density is associated with high levels of calciprotein particles in patients with Fabry disease," was published in the journal *Osteoporosis International.*

Studies have indicated that people with Fabry, particularly men, also have higher rates of diseases characterized by bone mineral density loss, such as osteoporosis or osteopenia. However, the biological mechanisms by which the bone mineral density is lower in Fabry patients have not been fully explored. The levels of CPP in the bloodstream have correlated with disease-related processes related to chronic kidney disease, a common feature in Fabry. High levels of circulating CPPs also have been reported in other chronic inflammatory disorders such as inflammatory bowel disease and inflammatory joint conditions.

Read full story: bit.ly/fabrybones

Europe teens report high Fabry burden despite ERT

By Marta Figueiredo, PhD
FabryDiseaseNews.com

(July 29, 2022) The Fabry burden is variable but significant among adolescents and caregivers, affecting their quality of life and mental health, according to results of online surveys in three European countries.

In addition, standard enzyme replacement therapy (ERT) was reported to reduce the disease's burden, but not fully. These findings highlight the significant impact of Fabry in teens and the urgent need for new, effective therapies and tailored approaches for each patient and their symptoms, the researchers noted.

The study, "Burden associated with Fabry disease and its treatment in 12–15 year olds: results from a European survey," was published in the *Orphanet Journal of Rare Diseases*.

While Fabry's burden has been well-explored in adults, there is limited evidence on the physical and emotional burden of the disease and ERT's impact in adolescents and their caregivers.

With this in mind, researchers at Amicus and Adelphi Values developed separate online surveys targeted to adolescents, 12–15 years, with Fabry, their caregivers, and healthcare professionals (HCPs) with experience with this patient population.

The surveys were conducted across the U.K., Germany, and France, from June to September 2021. Recruitment was performed by a third-party recruiter and with the help of patient advisory organizations.

A total of 14 patients (eight boys and six girls), 14 corresponding caregivers (11 women and three men; nine also with Fabry), and five HCPs were surveyed.

Results showed that symptom burden was high in adolescents with Fabry, with "pain" and "intolerance to heat or cold" being among the most commonly reported symptoms, both by patients and healthcare professionals. Nearly half of the adolescents also reported always sweating less than normal, and more than a third said they felt burning sensations in the hands and feet at all times.

"There were high levels of reporting across the symptoms indicating on overall high and varied symptom burden," the researchers wrote. The severity and frequency of symptoms had a large impact on the adolescents' quality of life, with a severe impact being reported by patients who also reported more severe symptoms.

Notably, there was an agreement between symptoms and factors contributing to treatment decisions.

Study: Fabry possible cause of kidney disease in children

By Steve Bryson, PhD
FabryDiseaseNews.com

(July 1, 2022) A rare case of end-stage kidney disease was discovered in a young boy with Fabry disease, a case study reported. In such cases of unexplained kidney failure in children, a detailed family history should be taken, and Fabry considered a possible cause, the researchers recommended.

The case study, "Early renal failure in childhood in a male with Fabry disease," was published in the journal *BMJ Case Reports*. Kidney failure due to chronic kidney disease is a late complication, mainly occurring about the fifth decade of life, among those with classical Fabry. It is very rarely seen in children.

In this report, researchers at University College London, in the U.K., describe the case of an 11-year-old boy who developed kidney failure due to undiagnosed Fabry. The boy ultimately required dialysis and a transplant.

Upon examination, he had many signs and symptoms of Fabry, including episodes of severe pain and burning, decreased sweating, digestive tract symptoms, and eye deposits. The child also had clusters of small reddish or dark-blue spots on the skin, called angiokeratomas. Blood tests revealed high urea and creatinine levels, both indicators of chronic kidney disease.

Based on these findings, the boy was started on kidney dialysis while tests were performed to determine the cause of his kidney failure. A kidney biopsy showed deposits in the lysosomes. He had low levels of Gal A in his bloodstream and immune cells and an unusual mutation in the GLA gene that encodes for the Gal A enzyme.

Read full story: bit.ly/fabrycause

Testing for Tots celebrates 4 years with wine fundraiser

By Tia Rosenbalm
FSIG Contributor

Sept. 16 marked the 4th year since Brian and Tia Jones launched Testing for Tots as a program with FSIG. Testing for Tots' mission is increasing early diagnosis of Fabry disease primarily through expansion of newborn screening for Fabry disease.

A Tasting for Testing for Tots is our annual fundraising and awareness event. This year we celebrated our fourth year with a fun night of music, wine tasting and fundraising, highlighted by an excellent silent auction.

Testing for Tots is currently working toward individual state newborn screening expansion. With this, we seek to empower the Fabry community through early diagnosis of our youngest members and subsequently diagnosed family members (on average five per newborn diagnosed).

We are passionate about expanding the benefits of newborn screening to the 44 states currently not checking for Fabry. Together, we can give a voice to the 97% of undiagnosed and untreated people living with Fabry.

PHOTOS COURTESY OF TESTING FOR TOTS

Brian and Tia at the event, held in Greenville, SC.

In 2022, Testing for Tots has presented to Georgia's and Utah's Newborn Screening Committees, celebrated with New Mexico—which started screening for Fabry July 1—and has its eyes set on co-founder Brian Jones' home state of South Carolina. If you live in SC, we need your family Fabry story to share with legislators! Please email us at testingfortots@gmail.com if you are willing to progress newborn screening in SC!

Fabry father sets world record for wheelchair speed

By Melissa James
FSIG Contributor

His first came in 2020, when he blew away the previous record for fastest electric wheelchair in the world. Then on Aug. 1, he recorded a new record, this time in a specially adapted head-controlled wheelchair.

Liversidge was already suffering from Fabry, which both his daughters have inherited. But in 2013, he learned he also had a new, incurable condition where the cells in his brain and nerves, called motor neurones, stop working. The condition has left him paralyzed from the neck down.

He opted for a tracheotomy two years ago to prolong his life, and in May survived a heart attack.

While awaited the Guinness certification, the expectation is that Liversidge will be confirmed as the world record holder for the fastest head-controlled electric wheelchair. During his recorded attempt, his average speed was clocked at 41.8215 miles per hour.

His wife, Liz, subsequently posted on social media: "Despite having two terminal illnesses, being paralysed from the neck down and tracheostomy ventilated, Jason Liversidge has achieved the impossible, a second world speed record for the Fastest Head Controlled Electric Wheelchair. A huge thank you to everyone who supported him and made the impossible possible."

In an email UK website Hull Live before his first world record, he said that his daughters Lilly and Poppy were the inspiration for his endeavor: "I have always had a passion for speed. I can no longer drive a car or ride a motorbike; however, I can drive an electric wheelchair ... "I am keen to set a world record because I want to leave a legacy for my girls."

According to the website, his other achievements in the years since his 2013 diagnosis include climbing Mount Snowdon in a wheelchair and abseiling off the Humber Bridge.

Read full story: bit.ly/fastdad

FSIG

FSIG is a support group dedicated to dispensing information and encouraging mutual self-help as a means of emotional support.

FSIG was formed in 1996 by two Fabry patients and supportive family members with the hope that their particular understanding of this disease, combined with experience gathering information and working with doctors could benefit others.

FSIG is a nonprofit, tax-exempt organization and relies on charitable contributions to provide services to those with Fabry disease, their families and supportive others. Donations may be sent to the address below.

Please feel free to make copies of the FSIG Newsletter to share with your family, friends and others. We encourage anyone interested in FSIG or the newsletter to contact us so we can make sure you receive the next issue.

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Patients wanted to test device for detecting cardiac problems in Fabry

By Mary Chapman
FabryDiseaseNews.com

(July 15 2022) A clinical study in the U.K. is recruiting adults with Fabry disease (FD) to determine whether implantable loop recorders (ILRs)—a device for continuous heart monitoring—can improve arrhythmia detection and identify risk predictors for cardiac problems.

Participants' heart rhythms will be tracked, using the surgically implanted device, for three years—"giving a potential opportunity to offer treatment at an earlier stage" to Fabry patients with cardiac problems, the researchers noted. All monitoring will be done remotely.

"Patients with Fabry disease are living longer and with a better quality of life. We want to further improve cardiac outcomes [for] patients with Fabry," the team stated in a press release.

The study, "Arrhythmia Burden, Risk of Sudden Cardiac Death and Stroke in Patients with Fabry disease: the Role of Implantable Loop Recorders (RaILRoAD)," is seeking up to 164 Fabry patients who are at least 18 years old and have evidence of heart disease. Recruitment ends Aug. 1.

Led by University Hospitals Birmingham, the RaILRoAD study (NCT03305250) is recruiting patients at its West Midlands center, as well as at the Salford Royal Hospital, in Manchester, and the Sheffield Teaching Hospitals. Two other centers in the U.K., and an additional site at the University of Sydney, in Australia, are not yet recruiting.

The open-label, randomized controlled trial is being touted as the first to evaluate arrhythmia—simply put, an irregular heartbeat—and the use of ILRs across risk profiles in Fabry cardiomyopathy. The hope is that this study will enable detailed characterization of arrhythmic risk predictors in Fabry and, ultimately, support the formulation of disease-specific guidance for high-risk patients.

Read full story: bit.ly/cardiactest

CARS microscopy technique may identify heart involvement

By Marisa Wexler, MS | FabryDiseaseNews.com

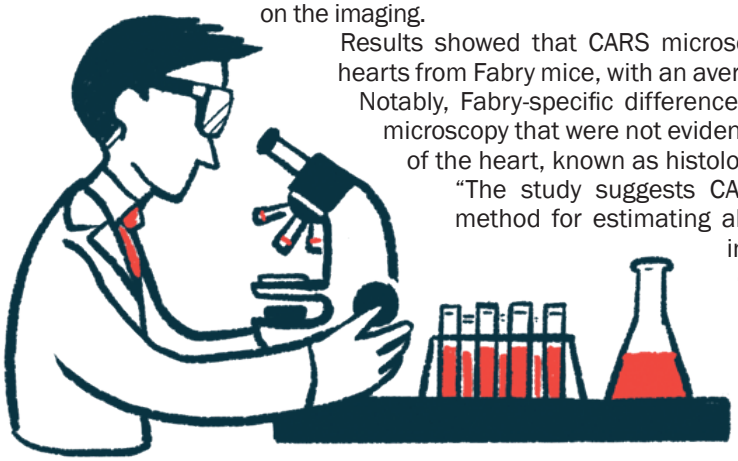
(June 24, 2022) Fabry disease is characterized by the buildup of certain fat molecules, called lipids, that can affect many bodily tissues, including the heart. Heart involvement is a leading cause of mortality in Fabry, and it often takes a long time to identify.

Thus, finding ways to more quickly identify heart disease in people with Fabry could allow for better-tailored treatment strategies.

CARS microscopy is an imaging technique that, very simplistically, involves analyzing how molecules in tissue vibrate when two laser beams are shined on a sample. Lipids—including the molecules whose buildup characterizes Fabry—characteristically have long hydrocarbon "tail" structures, which usually produce strong vibrational signals when analyzed via CARS microscopy.

Results showed that CARS microscopy could effectively identify hearts from Fabry mice, with an average sensitivity as high as 96%.

Now, researchers in Germany used the technique to analyze heart tissue from mice with or without Fabry disease. The team used a battery of machine learning techniques to make sense of the raw data generated by CARS. That allowed a computer to "learn" how to differentiate Fabry from non-Fabry cases based on differences in patterns on the imaging.



Results showed that CARS microscopy could effectively identify hearts from Fabry mice, with an average sensitivity as high as 96%. Notably, Fabry-specific differences could be detected by CARS microscopy that were not evident with standard tissue analysis of the heart, known as histological staining.

"The study suggests CARS microscopy as a reliable method for estimating abnormal [lipid] accumulations in certain organs of [Fabry disease] even if they are not yet detectable by standard histological staining," the researchers wrote.

Read full story: bit.ly/CARSheart

Galafold safe, effective at reducing heart damage

By Marta Figueiredo, PhD
FabryDiseaseNews.com

(June 3, 2022) Galafold (migalastat) is generally safe and significantly reduces disease-associated heart enlargement in Fabry disease patients carrying Galafold-amenable mutations, according to two-year data from a real-life, multicenter study in Germany.

These benefits were generally similar between patients who had previously received standard enzyme replacement therapy (ERT) and those who had not.

Patients' kidney function did show a significant decline over the two years, particularly among patients on certain medications for high blood pressure (hypertension), suggesting they had a higher disease burden at the start of treatment.

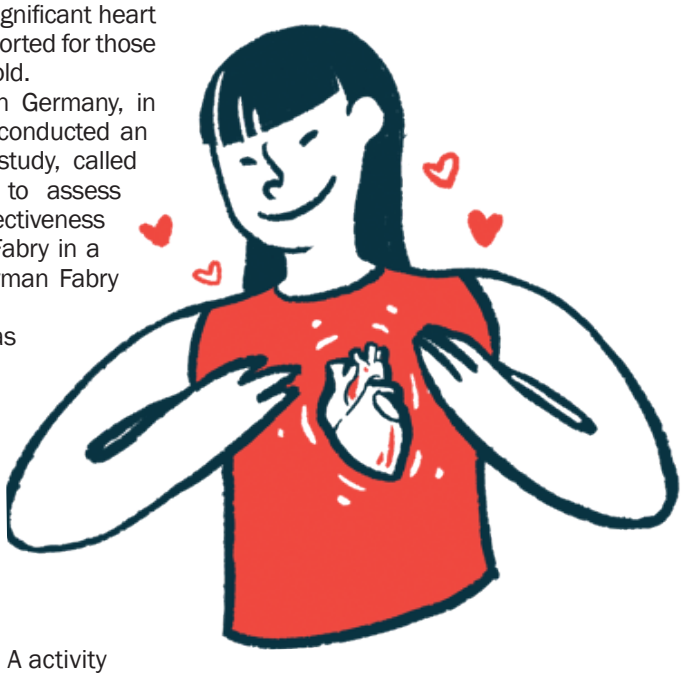
These findings generally support Galafold for treating Fabry among eligible patients, but physicians should monitor the clinical response on a regular basis, the researchers noted.

The study, "Treatment of Fabry Disease management with migalastat—outcome from a prospective 24 months observational multicenter study (FAMOUS)," was published in the *European Heart Journal – Cardiovascular Pharmacotherapy.*

Previous clinical and real-world studies have shown Galafold's safety and effectiveness in Fabry patients with amenable mutations, and significant heart improvements were also reported for those switching from ERT to Galafold.

A team of researchers in Germany, in collaboration with Amicus, conducted an observational, multicenter study, called FAMOUS (NCT03135197), to assess the two-year safety and effectiveness of Galafold in people with Fabry in a real-world setting. Nine German Fabry centers were involved.

The study's main goal was to assess changes in heart enlargement—as assessed with left ventricular mass (LVM)—and kidney function, measured through the mean annualized change in the estimated glomerular filtration rate (eGFR). Patient-reported outcomes and levels of Gal A activity and lyso-Gb3 were also assessed.



As of July 2020, data was available for 54 patients (26 females and 28 males), with a mean age of 45. Nearly two-thirds (61.1%) had been previously given ERT, most commonly Replagal (60.6%).

Hypertension was present in 31 (57.4%) patients and 37 (69.8%) were on anti-hypertensive medication to reduce blood pressure and/or protect the heart and the kidneys. Females tended to more often experience Fabry-associated pain than males (76.9% vs. 50%).

Results showed Galafold was generally safe and well tolerated, with no severe treatment-related side effects reported. There were 17 clinical events (all related to cardiovascular problems) and only a mild adverse event of vomiting right after Galafold was initiated, which was resolved with ongoing treatment.

Read full story: bit.ly/galafoldheart

ECG parameter may help ID Fabry patients at risk for pacemaker

By Marta Figueiredo, PhD
FabryDiseaseNews.com

(May 27, 2022) Many Fabry disease patients with heart involvement develop a slow and irregular heartbeat, called bradyarrhythmia, late in the disease course when heart damage is already advanced, according to a small study in Italy.

The finding adds to previous studies reporting bradyarrhythmia as a late symptom of Fabry, discouraging its use as marker for the early identification of the disease, the researchers noted.

Follow-up variations in QRS, a parameter of electrocardiogram (ECG), were strongly associated with bradyarrhythmia onset and the future need for a pacemaker, highlighting that regular ECG assessments are important for people with Fabry.

A pacemaker is a small device that's surgically implanted in the chest to help control a person's heartbeat. It's usually recommended for people with irregular and/or slower-than-normal heartbeat.

The study, "Prevalence and predictors of bradyarrhythmias requiring permanent pacing in patients with Anderson–Fabry disease," was published in the form of a brief communication in the *Journal of Cardiovascular Electrophysiology*.

More than 50% of Fabry patients show heart involvement, which usually manifests as left ventricular hypertrophy (LVH), irregular heartbeat (arrhythmias), heart scarring, and functional problems, and is the leading cause of death. LVH refers to the enlargement and thickening of the walls of the heart's main pumping chamber.

As such, identifying markers leading to early diagnosis of Fabry and early detection of heart involvement is crucial to prevent further damage. In patients with heart damage, "easy and cost-effective markers of risk for [pacemaker] requirement may help prevent clinical complications, including [fainting] and sudden death," researchers wrote.

Men showed overall more severe heart disease than women and were more likely to die (23% vs. 1.9%) during follow-up.

Read full story: bit.ly/fabryecg

NEWS BRIEFS

Study: COVID creates no extra Fabry-related risks

(Aug. 5, 2022) The risk of severe COVID-19 in people with Fabry disease appears to be driven by immune system function rather than by the genetic disorder itself—"similar to the general population"—a small study concluded.

"Immunosuppression therapy in kidney transplant recipients represented the highest risk in this [patient] population," the researchers wrote.

Further studies on Fabry disease and COVID-19 may reveal potential protective responses in these patients that could be of interest for future treatments, the researchers noted.

"Our finding, that kidney transplant recipients suffered most from severe COVID-19 is of particular importance regarding vaccination strategies," the researchers wrote. "More specifically, it is known that the different immunosuppressive medications impair or suppress the response to vaccination via multiple mechanisms."

Read full story: bit.ly/fabrycovid

Federal judge strikes down CMS' Medicaid copay rule

(May 19, 2022) A federal judge struck down a controversial rule that requires drug companies to include copay assistance like coupons into Medicaid rebates, handing the pharmaceutical industry a major win.

The ruling, delivered Tuesday in the U.S. District Court for the District of Columbia, deals a major blow to insurers and pharmacy benefit managers (PBMs) that have adopted copay accumulator programs that limit the impact of drugmaker assistance from counting toward the deductible and out-of-pocket caps, arguing that the assistance is meant to drive patients to more expensive drugs.

The ruling focuses on a Centers for Medicare & Medicaid Services rule finalized in December 2020 under the Trump administration. The regulation, which goes into effect next year, said that any copay assistance like coupons or other cost-sharing help must be included in the calculation of the best price of the drug.

Read full story: bit.ly/cmscopay

'Once-in-a-generation' prescription drug pricing reform could be coming.

(July 29, 2022) CNBC reports that the Senate reconciliation bill put forward by Senate Majority Leader Chuck Schumer, and Sen. Joe Manchin has the goal of helping give Americans relief from rising health-care costs. CNBC identified as the key points:

- The Democratic reconciliation package that addresses climate and taxes also includes changes that are aimed at paring back health-care costs.
- That includes letting Medicare negotiate the costs of prescription drugs and limiting price increases on medicines.
- "It will ensure that drug companies will no longer be able to raise prices faster than the rate of inflation," one lawmaker said.

Late-onset Fabry may be more common after all

(Sept. 23, 2022) Mutations likely to cause Fabry disease, particularly those associated with late-onset disease, were found to be more common in an adult population of U.K. residents than the estimated prevalence of the disease itself, a genetic analysis showed.

The findings suggest late-onset Fabry disease prevalence may be higher than estimates, according to researchers.

The study, "Prevalence of Fabry disease-causing variants in the UK Biobank," was published in the *Journal of Medical Genetics*.

Mutations that lead to less than 3% of normal enzyme activity cause the classic, more severe type of Fabry disease, which usually develops in childhood or adolescence. Mutations generating an enzyme with some residual activity (3%–15% of normal) lead to a later, somewhat less severe form of the disease.

Current estimates for the global prevalence of Fabry disease range from one in 40,000 people to one in 170,000. Newborn screening studies suggest the number is higher.

Read full story: bit.ly/lateFabry

National screening leads to more Fabry diagnoses in the Czech Republic

(Sept. 30, 2022) Implementing nationwide screening programs for Fabry disease in people with a heart condition called hypertrophic cardiomyopathy (HCM) may help improve diagnosis of the disease, a study in Czech Republic shows.

In the country, the program led to the diagnosis of Fabry in four men and two women among the 589 HCM patients screened. These findings also highlight the importance of screening both sexes, the researchers noted, as the disease shows milder symptoms in women, who are more difficult to diagnose, than in men.

The program and its results were described in a study, "Nationwide screening of Fabry disease in patients with hypertrophic cardiomyopathy in Czech Republic," published in *ESC Heart Failure*.

Read full story: bit.ly/CzechFabry

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