SUMMER 2023

FSIG Connection

News from the Fabry Support & Information Group

INSIDE

FIN features "Fabry heroes" for awareness month

By Mary Chapman
FabryDiseaseNews.com

(April 6, 2023) For this year's Fabry Awareness Month—observed every April to bring attention to Fabry disease—the spotlight is on the everyday heroes who live with the rare genetic lysosomal storage disorder.

Activities during the month are aimed at heightening awareness among the general public, in addition to lawmakers, public authorities, researchers, industry representatives, and health professionals.

To celebrate patients and call attention to their journey, the Fabry International Network (FIN)— which supports 60 patient organizations in 57 countries—is presenting a "Fabry Heroes" campaign.

"By giving people with Fabry a superhero mask, we applaud their strength, courage, and never-give-up attitude," the organization states on an awareness month webpage. "Join FIN in celebrating the

See HERO, page 3

FDA OKs PRX-102 to treat Fabry

Now named Elfabrio, delivers functional GalA to bloodstream

By José Lopes, PhD
FabryDiseaseNews.com

(May 10, 2023) PRX-102 (pegunigalsidase alfa) has been approved by the U.S. Food and Drug Administration (FDA) to treat adults with Fabry disease.

Now branded Elfabrio (pegunigalsidase alfa-iwxj), the enzyme replacement therapy (ERT) is to be given as an intravenous, or into the vein, infusion every two weeks. It was codeveloped by Protalix BioTherapeutics and Chiesi Global Rare Diseases. The recommended dosage is 1 mg/kg.

"We are extremely pleased to receive FDA approval of ELFABRIO for the treatment of adult patients with Fabry disease," Dror Bashan, Protalix's president and CEO, said in a press release. "This approval is a testament to the dedication of the Protalix and Chiesi teams to deliver this much needed new therapeutic option to patients in need."

The FDA rejected a request in 2021 for PRX-102's accelerated approval, citing issues with the manufacturing process and facility inspections. No issues were raised about safety or effectiveness.

See ELFABRIO, page 2

WELCOME

Dear Friends,

Great news for the Fabry community! PRX-102, which is now ELFABRIO®, has received FDA approval for the treatment of Fabry Disease. Congratulations to Chiesi and Protalix on this achievement!

With 7.5 years of clinical treatment of over 140 patients, ELFABRIO® has proven to be another effective treatment to slow the progression of Fabry. With so many variables in both men and women, adding a new therapy advances the screening and treatment for our disease.

A big thank you to the many people that volunteered and participated in these trials.

Jack

Jack Johnson, Executive Director

Man's colon removed without surgery

By Patricia Inácio, PhD
FabryDiseaseNews.com

(June 9, 2023) A 55-year-old man with a Fabry disease-related tumor in the large intestine was treated successfully with a nonsurgical procedure called endoscopic rubber band ligation therapy, a case study reported.

"[C]olonoscopy surveillance may benefit Fabry's disease patients with gastrointestinal [obstructions]," researchers wrote, adding that rubber band ligation therapy is a viable alternative to surgery in these situations.

The report, from University Hospital Würzburg, Germany, describes the case of a patient who was undergoing treatment with Galafold (migalastat), and who had experienced weight loss, abdominal discomfort, distension, bloody stools, and irregular bowel movements for six months. A colonoscopy found a 40mm obstructive tumor in the colon.

Pro-kinetic medications, commonly used to enhance gastrointestinal motility and improve the movement of food through the digestive system, is not advised for Fabry patients.

So physicians opted for colonoscopy endoscopic rubber band ligation therapy instead of surgery. This procedure involves placing small rubber bands at the base of abnormal tissue or lesions to constrict its blood supply, causing it to shrink or fall off with time.

The treatment was performed over three sessions at three-month intervals, which culminated in the successful removal of the tumor and the relief of symptoms, as confirmed in a three-month follow-up. The colon was shortened due to scarring.

Read full story: bit.ly/ColonTumor

ELFABRIO, continued from page 1

"While much progress has been made in the treatment of Fabry disease, there is still a need for new treatment options," said Giacomo Chiesi, head of Chiesi Global Rare Diseases. "We established Chiesi Global Rare Diseases to deliver innovative therapies and solutions for people affected by rare diseases. With the FDA approval of ELFABRIO, we can now offer people living with Fabry disease an alternative treatment option."

A second biologics license application (BLA) was submitted last year. The decision in the U.S. follows a recent approval by the European Commission.

"The European Commission's approval of PRX-102 is a significant milestone for patients with Fabry disease and their families, providing a new therapeutic option," Bashan said at the time. "We are proud of this achievement and believe that this approval further validates our science and technology."

How does Elfabrio work?

PRX-102 delivers a functional version of Gal A via infusion into a patients' bloodstream. Created with Protalix's plant-based ProCellEx platform, it's been chemically designed to provide a long half-life, that is, the time required for the blood level of a medication to reduce by half.

The evidence supporting the FDA's approval comes from a comprehensive program in more than 140 patients spanning up to 7.5 years of follow-up, according to its developers.

One of the studies that was part of the resubmitted BLA, the Phase 3 BALANCE clinical trial (NCT02795676), compared PRX-102 to Sanofi Genzyme's approved ERT Fabrazyme (agalsidase beta) in adults with Fabry disease and impaired kidney function. Both therapies were given by infusion every two weeks. After two years, PRX-102 and Fabrazyme were similar in safety and effectiveness at preventing kidney function decline. PRX-102 was also well tolerated.

The other completed studies were two Phase 3 trials—BRIDGE and BRIGHT—and a Phase 1/2 trial along with its extension study. In the BRIDGE and BRIGHT studies, patients previously on Fabrazyme or Replagal (agalsidase alfa, an ERT marketed by Takeda) switched to PRX-102, which was given every two weeks in BRIDGE and every four weeks in BRIGHT. Results indicated PRX-102 maintained or at least slowed kidney function decline.

Safety data that originated from the ongoing extension studies of these trials (NCT03566017 and NCT03614234) also were included in the second BLA.

Chiesi and Protalix note clinical trials haven't established that an extended ERT half-life is associated with superior effectiveness or safety.

"The totality of clinical data suggests that Elfabrio has the potential to be a long-lasting therapy," Bashan said. "Together with Chiesi, we are grateful to all of the patients and investigators and their staff members who participated in our clinical trial programs and remain committed to bringing Elfabrio to patients with Fabry disease."

"It is important to understand that there is a lot of variability in Fabry disease and misdiagnoses are common, especially in women," said Jack Johnson, founder of the Fabry Support & Information Group (FSIG). "Growing up, a lot of people didn't know what was wrong with me. They knew I was different, but they didn't know why. Now we have made advances in screening, treatment, and monitoring for Fabry disease."

Read full story: bit.ly/Elfabrio

FSIG Connection debuts caregiving column

Meet Kallie Wingate—adopted into a Fabry family and writing about their care

ON THEIR SIDE

By Kallie Wingate

Family is such an important thing for me. I wouldn't be who I am today if not for my family. Family brings me joy and laughter. It brings hope and peace of mind. My family lifts me up and makes sure I know that I'm always loved and supported.

But with all of that good comes some hard times. My grandmother, Joyce Burley (whom I call Nanny) says everybody is going through something. For my family, that something is Fabry disease.

I myself don't have Fabry disease. I was adopted into the family when I was 6 months old—but that doesn't mean it hasn't become a huge part of my life. My dad, Michael Burley, did have Fabry disease, and I was one of his biggest fans. He was very goofy, but he had the biggest heart.

From other people's eyes, though, he probably wasn't someone to look up to. Due to his complications from Fabry, as well as his mental health, he had trouble keeping a job.

But I saw him as the best dad I could ever ask for. He made me laugh at times when I didn't think I could. I never doubted that he loved my brothers and me. He always said that his biggest accomplishments were his children. He was a proud dad, and I was a proud daughter.

We lost my father in October 2020, from Fabry complications. This was less than a year after the death of my Uncle Billy, who also lost his battle with Fabry. My entire family was devastated, and we still grieve their losses to this day.

I try to do the best I can to honor my dad and Uncle Billy by advocating and spreading the word about Fabry disease whenever I get the chance. Nanny says spreading the word is the best thing I can do to help those with Fabry. She has taught me so much over the years. She has always taken such good care of this family, even through her own Fabry battle. I couldn't be more grateful for her. My family tries to deal.

We try to laugh more than we cry. My family is one big mess—but it's my mess, and I wouldn't change it for the world!

COURTESY OF KALLIE WINGATE

Kallie stands proud on the side of her beloved Nanny, aka Joyce Burley.

This column is named "On Their Side" because loved ones who don't have Fabry have to watch it from the sideline; because loved ones are often giving care at the side of the person suffering; and because loved ones are often the biggest Fabry advocates—always on their side.

HERO, continued from page 1

#FabryHeroes and share their brave stories. Let's spread awareness and show our appreciation together!"

Supporters are asked to engage with FIN on social media during the month and share the group's posts, using the hashtag #FabryHeroesMonth.

"Simply liking, sharing, and commenting on our posts about Fabry Heroes can make a big difference in spreading awareness and educating others," the organization states.

Awareness month participants also are encouraged to share their own messages of support to spark conversation about the disease and the annual event.

FIN also is offering prepared social media posts, each including a patient photo, about Fabry Heroes that participants can download and use on their platforms. One such post features 24-year-old Amira, of Morocco, who wrote: "Fabry disease has an impact on my life, in ways I can not control. Even so, I take my health into my own hands. There are so many things I can do to enhance my qualify of life."

There's also patient Ji-woo, 19, of South Korea, who wrote: "I used to be focused on everything I can't do because of Fabry. Conversations with other people with Fabry changed that. By setting my own limits and believing in myself I can achieve so much more."

Mary, 55, from the U.S., says she's "very grateful" for her Fabry family.

"Meeting other people with Fabry gives me energy. We automatically have a bond, because we have this rare disease in common," she wrote.

Throughout April, FIN is featuring Fabry "heroes" on Facebook. The National Fabry Disease Foundation is tweeting daily about the disorder and sharing community information.

Survey: Patients prefer at-home ERT

Patients say it saves them time, money in traveling to the clinic

By Patricia Inácio, PhD
FabryDiseaseNews.com

(April 28, 2023) Patients prefer receiving enzyme replacement therapy (ERT) at home, citing savings in travel time and cost, over clinical visits, according to a survey of people with Fabry disease and other lysosomal storage disorders in Germany.

"All patients would recommend home-based ERT to other patients" during the two-year follow-up study.

The study, "The patients' perspective on home-based infusion: A longitudinal observational study in the German healthcare setting for patients with lysosomal storage disorders treated with enzyme replacement therapy," was published in the journal *Molecular Genetics and Metabolism Reports.*

ERT for Fabry delivers a lab-made version of the Gal A enzyme directly to the bloodstream. The treatment can be administered at specialized centers or at home by a nurse.

At-home administration makes it easier for patients to carry out their daily routines, which likely helps them to adhere to the treatment. In several countries, including the U.S., ERT is routinely given at home, but in Germany, most patients still receive ERT in specialized centers, hospitals, or doctors' offices.

Data about how patients feel about these treatment options is limited in Germany. Thus, researchers interviewed a group of 30 patients (mean age 39.9 years; 19 males) with a lysosomal storage disorder who began home-based ERT, after being treated at medical clinics. The study covers the period from January 2019 to June 2021, and included 18 patients with Fabry disease, five with Gaucher disease, six with Pompe disease, and one with mucopolysaccharidosis type 1.

Patients were interviewed before the start of their first home-based ERT and then at regular intervals thereafter —at six, 12, 18, and 24 months. Among those with Fabry with information about their condition, eight had the classic form of the disease with several organs affected, four had predominantly cardiac manifestations, two had a mild form, and one had kidney issues mainly.

Among the overall group of participants, 14 reported other conditions, the most common being hypertension (high blood pressure) and heart disease. Before transitioning to home infusions, 10 patients received their ERT in the hospital, six in a specialized center, and 14 patients as outpatients. On average, 12 reported waiting less than 30 minutes to receive their ERT, and eight patients reported between 30 and 90 minutes of waiting time. One patient reported waiting longer than 90 minutes. The remaining nine patients reported no waiting time.

Infusion took, on average, 2.7 hours (range of 50 minutes to five hours). Most patients (73.3%) arrived at the clinic by car. Travel costs were completely reimbursed by the health insurance for 10% of the patients, with one patient having a co-payment. The majority (86.7%) supported the travel costs themselves or with help from family members.

In the previous three months, six patients had postponed at least one ERT session.

All participants felt they were adequately informed about their condition and treatment options. Twenty-two patients indicated they always felt well cared for by their ERT provider.

Read full story: bit.ly/FabryHome

Optimized versions of Gal A enzyme may pave way to better treatments

Modified enzymes last longer in blood, show better tissue activity

By Lindsey Shapiro, PhD
FabryDiseaseNews.com

(March 31, 2023) Scientists have engineered versions of the alpha-galactosidase A (Gal A) enzyme that could eventually be used to produce a more stable and effective enzyme replacement therapy (ERT) for Fabry disease.

In animal models, the modified enzymes lasted longer in the bloodstream and showed better activity in target tissues like the heart and kidneys. In cell cultures, they demonstrated they may be less likely to evoke an immune response against Gal A that can reduce a person's responsiveness to treatment.

Although more long-term research is still needed, scientists say the enzymes could possibly "address the therapeutic shortcomings of [Gal A] for the treatment of Fabry disease," with the potential ability to "reduce the dosing frequency or increase the efficacy for an enzyme replacement therapy."

The study, "Optimizing human α-galactosidase for treatment of Fabry disease," was published in the journal *Scientific Reports.*

ERT is a mainstay treatment that works by providing patients with a lab-made version of the Gal A enzyme they lack. There are currently two approved ERTs — Sanofi's Fabrazyme and Takeda's Replagal — both of which have shown to slow disease progression.

However, existing ERTs are cleared rapidly from the bloodstream, meaning patients require frequent into-the-vein infusions, and even still may experience significant symptoms. This rapid clearance may mean that the treatments don't get to key target tissues like the heart and kidneys, researchers suggested.

Moreover, for patients who lack their own GLA enzyme, their immune system may launch an attack against the therapy, rendering it less effective.

In the study, the scientists looked for ways of modifying the Gal A protein sequence to improve its performance. Essentially, they introduced different mutations to the GLA gene that would produce various working versions of the protein.

After screening more than 12,000 of them in yeast and cell cultures, the team identified two in particular that might be able to increase Gal A's stability and lessen the risk of immune responses.

One version, GLAv05, housed 11 mutations that differed from the typical enzyme, and the other, GLAv09, had 17 mutations. Both were found to be more stable than standard Gal A.

In human blood samples, each modified enzyme retained more than 90% of its activity after 24 hours, whereas standard Gal A retained less than 10% activity in the same window.

GLAv09 also exhibited significantly higher enzyme activity in cells from Fabry patients, with a 19-fold higher activity than Gal A after a week that corresponded to a 10-fold greater reduction in Gb3 buildup.

The benefits of GLAv05 weren't as robust, suggesting its cellular uptake may be impaired relative to GLAv09, the researchers suggested.

Overall, the increased stability and cellular uptake of the modified enzymes translated to sustained enzyme activity in animals.

Read full story: bit.ly/OptimizedGalA

Galafold may reduce heart changes, boost exercise tolerance

By Patricia Inácio, PhD
FabryDiseaseNews.com

(Feb. 23, 2023) In previously untreated Fabry disease patients with heart involvement, 18 months of treatment with Galafold (migalastat) stabilized measures of heart disease and was linked to a trend toward improvement in exercise tolerance, an observational study reported.

These findings provide "new detailed evidence on the effect of migalastat on FD [Fabry disease] cardiomyopathy [heart disease]", the researchers wrote. "This information can help clinicians in managing therapeutic options for patients with FD."

The study, "Effect of Migalastat on cArdiac Involvement in FabRry Disease: MAIORA study," was published in the *Journal of Medical Genetics*.

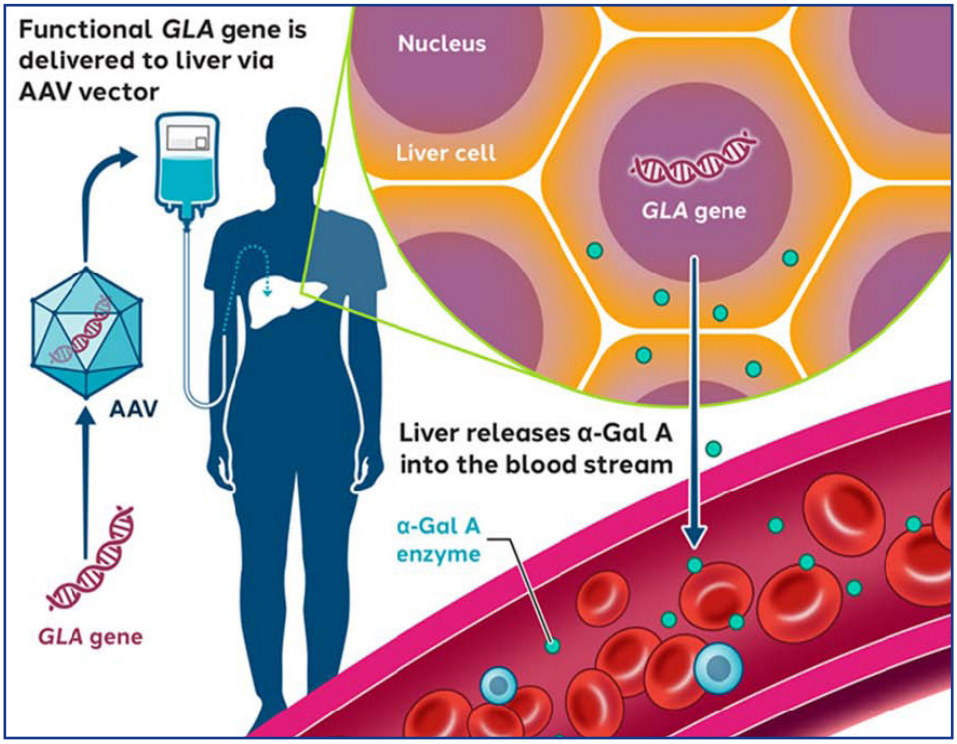
Heart involvement is common with Fabry disease. One feature linked to heart disease is an increase in left ventricular mass (LVM), the estimated weight of the heart's left lower pumping chamber.

A previous study, assessing LVM by echocardiography—an ultrasound of the heart—revealed a small, but significant reduction after 18 months of Galafold, an oral chaperone therapy developed by Amicus Therapeutics that restores alpha-galA activity in patients carrying specific GLA mutations, referred to as "amenable." A follow-up study with a large group of patients confirmed these findings.

Read full story: bit.ly/Gala-heart

Emory team testing Fabry gene therapy

By Quinn Eastman
Emory University News Center



(March 20, 2023) For years, the phrase "gene therapy" sounded like science fiction.

Now it's become reality for a number of diseases as researchers refine once-experimental approaches. Emory's Genetic Clinical Trials Center (GCTC) was designed as a hub for testing the increasing number of products aimed at genetic diseases.

"Our goal is to bring the latest treatments to our patients sooner," says William Wilcox, MD, PhD, professor of human genetics at Emory University School of Medicine and GCTC investigator. "We work with a lot of different specialists and industry partners to bring these things to market so we can help our patients."

As part of a clinical trial testing a gene therapy for Fabry disease, Curtis Primus travels to Atlanta every month from Wisconsin. Along with other members of his family, Primus was diagnosed with Fabry disease as a child, based on characteristic streaks in the cornea of their eyes.

"It would feel like, when I'd slide a shirt on, it would feel like someone's running sandpaper all over my body, wherever the clothing was touching," Primus says. "Sometimes it would feel like they're pulling my skin off with pliers."

COURTESY OF EMORY

Curtis Primus travels to Atlanta every month for the clinical trial. He describes his experiences and motivations in this video: bit.ly/curtis-video

Primus is part of a clinical trial evaluating a viral vector, which is based on AAV (adeno-associated virus), a benign virus. Hundreds of clinical trials are underway involving AAV vectors, and a few products based on AAV vectors have been FDA approved, including gene therapies for spinal muscular atrophy and hemophilia B.

AAV acts as a vehicle for delivering a circle of DNA encoding the missing enzyme to the liver. The circles stay in the liver for years, but they do not become part of chromosomes and are not transmitted to children.

"If the viral vector makes enough enzyme, it will leak some outside of liver cells and travel to the rest of the body," Wilcox says. "How much that occurs remains to be seen. Can it make enough to treat the whole body, and for how long? That's why we're doing the clinical trials."

"If it's not going to help me, it's still going to advance education and research on Fabry disease," Primus says. "If this treatment fails after a few years, at least they know this didn't work and they can try something different."

Manufacturer Sangamo Therapeutics recently announced preliminary results in the Fabry gene therapy clinical trial. Levels of alpha galactosidase A were sustained in 13 people, and several recipients have been able to go off enzyme replacement therapy. The longest treated participant has been in the study for two years. Long-term data on more people is needed.

In the Fabry gene therapy study, four people have been infused with the viral vector at Emory, and 20 people are now participating across several sites in the United States, the United Kingdom and Australia.

Read full story: bit.ly/GTCloser

ST-920 gene therapy continues to show safety, efficacy in trial

By Lindsey Shapiro, PhD
FabryDiseaseNews.com

(March 18, 2023) Updated findings in an ongoing Phase 1/2 clinical trial of Sangamo Therapeutics' gene therapy ST-920 (isaralgagene civaparvovec) shows the treatment continues to be well tolerated and effective in adults with Fabry disease.

As of the Nov. 19 data cutoff date, all five treated patients enrolled showed normalized levels of alpha-GalA—the enzyme lacking in those with Fabry—and has been sustained for at least a year in the longest treated patients.

The trial, called STAAR, is still recruiting (NCT04046224) up to 48 adults, ages 18 and older, at sites in the U.S. and U.K.

"These updated preliminary results demonstrate the potential of [ST-920] gene therapy to address the most challenging symptoms of Fabry disease with a favorable tolerability and safety profile," said Jaya Ganesh, MD, one of the study's investigators and a professor of genetics at the Icahn School of Medicine at Mount Sinai.

ST-920 is designed to deliver, through a one-time infusion, a healthy version of the GLA gene to the liver, allowing a fully functional alpha-GalA enzyme (a protein that acts as a catalyst) to be continuously produced.

The STAAR study is enrolling Fabry patients who are on ERT, have stopped ERT for at least six months, or who never used this treatment (ERT-naïve).

Across all three doses, ST-920 remains well-tolerated, with few adverse effects reported.

Read full story:
bit.ly/ST920Impact

Genetic testing recommended for family members of Fabry patients

Early diagnosis and treatment can improve life span, quality of life

By Marisa Wexler, MS
FabryDiseaseNews.com

(March 16, 2023) Testing family members of people diagnosed with Fabry disease can identify new individuals with the condition and improve their health outcomes, a recent study highlights.

"Family screening is of great significance in finding new patients with [Fabry disease]," the researchers wrote. "Therefore, genetic counseling should be recommended to all families with [Fabry disease] patients."

The study, "Clinical evaluation, accurate diagnosis and treatment of four pedigrees with Fabry's disease," was published in the journal *Frontiers in Pediatrics*. In genetics, a pedigree refers to a group of people who are biologically related to each other.

In this study, a team of scientists at Chengdu Women's and Children's Central Hospital, in China, reported the clinical characteristics of five children who were diagnosed with Fabry disease at their center from October 2021 to May 2022.

Among the five children (four males and one female), the age at diagnosis ranged from about 1 year to just over 13 years. Three had classic Fabry, while the other two were diagnosed with late-onset disease.

The oldest patient was diagnosed after several years of experiencing pain attacks. He also had an abnormally short stature and had not shown any signs of beginning puberty by age 13, which is unusual. Genetic and enzyme testing eventually led to a diagnosis of Fabry disease.

After the first patient was diagnosed, his 1-year-old half-brother was also tested and found to harbor the same disease-causing mutation. His mother was also found to be a mutation carrier.

Two of the other children were also diagnosed due to a family history of Fabry disease. One, with a history of intermittent foot pain, was diagnosed at the age of 6 after his mother and uncle were diagnosed with the disease. Another, who did not have any obvious symptoms, was diagnosed at age 7 after her father was found to have Fabry disease.

The fifth child in the report did not have any family history of Fabry. His mutation appeared to have developed de novo, meaning it was present only in him, but not in either of his parents. He was diagnosed as a toddler by genetic sequencing, which was ordered because he was unusually small for his age and was not growing at a normal rate.

The two patients diagnosed as infants and the 7-year-old who did not yet have any symptoms are being monitored, according to the researchers. The other two children have started on enzyme replacement therapy (ERT), and for both, treatment has helped to alleviate their symptoms.

"The early diagnosis, regular monitoring of confirmed cases in childhood, initiation of ERT treatment, and holistic lifestyle management can effectively prolong the life span and quality of life of patients," the researchers wrote.

Read full story:
bit.ly/FabryFamily

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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WORLD BRIEFS

UK court halts deportation of Egyptian with Fabry

(June, 2023) An Egyptian engineer with Fabry disease won a last-ditch attempt to prevent his removal from the UK.

Youssef Mikhaiel, 28, was due to be deported on May 28, but that was postponed after his case was taken to the Court of Session in Edinburgh.

He claims that if he were sent back to Egypt, he would not be able to access migalastat,which he receives in Scotland to treat his disease. Mikhaiel told BBC Scotland that he was still anxious because the threat of deportation was still on the table.

Mikhaiel arrived on a student visa in 2016 and graduated in aeronautical engineering at Glasgow University in 2019.

His visa expired the same year and he applied for leave to remain after he was diagnosed with Fabry. His application was refused over a failure to provide evidence in December 2021.

Read full story: bit.ly/deportFabry

Do rare diseases account for India's economic burden?

(March 18, 2023) The meaning of "rare" is "not occurring very often, but rare diseases are cumulatively not so rare anymore.

The landscape of rare diseases in India is continuously changing as new rare diseases and conditions are being recognized and reported regularly in the medical sector. In India, there is a lack of data on how many people suffer from rare diseases worldwide.

The cases recognized so far have been diagnosed at tertiary-level hospitals. The lack of data on rare diseases hinders understanding the extent of the burden of rare diseases and the development of a definition. In such cases, the economic burden of most rare diseases is unknown and cannot be appropriately estimated from the existing data sets.

So far, only a limited number of diseases have been recorded in India that are globally considered rare diseases through ambit may comprise 7000 to 8000 disorders.

Common reported rare diseases consist of:

- Primary immunodeficiency disorders
- Lysosomal storage disorders (such as Gaucher's disease, Mucopolysaccharidoses, Pompe disease, Fabry disease etc.)
- Small molecule inborn errors of metabolism (Maple Syrup urine disease, organic acidemias etc.),
- Osteogenesis imperfecta
- Cystic Fibrosis
- Duchenne muscular dystrophy, spinal muscular atrophy, etc.

Read full story: bit.ly/RareBurden

Malaysian father, schoolteacher battling Fabry

(April 26, 2023) A warm, sunny climate and abundance of delicious food sounds like paradise to many.

However, when hot weather leads to muscle cramps or fainting spells and kidney failure limits what you can eat, the picture becomes far less idyllic. This is what Merpati Ahmad, a 48-year-old schoolteacher, faces due to a rare disease known as Fabry disease.

For Merpati, the journey to a diagnosis took several years. While blood tests in 2008 revealed that he had high protein content in the urine, a sign of kidney disease likely caused by Fabry disease, he was only diagnosed with Fabry disease in June 2016 and received his first treatment in December 2018.

To treat Fabry disease, Merpati receives weekly enzyme replacement therapy which provides the enzyme his body needs, helping to reduce the build-up of fat, reduce pain and prevent further organ damage.

He finds that, since starting his treatment, he doesn't fall sick as easily as before.

Read full story: bit.ly/FabryMerpati

Korean Fabry patients demand insurance benefits

(April 18, 2023) Fabry Korea, surveyed its members this month to raise public awareness.

In the survey, 95 percent of Fabry disease patients and their family members experience a lowering of their quality of life due to the "negative consciousness of the genetic disease and psychological burden caused by lifetime treatment. Sixty-seven percent answered it exerts "very negative influence" and 28 percent pointed to "slightly negative influence."

The group explained that patients had trouble treating it and a sense of guilt for the genetic ailment and psychological burden. As the element that affected daily life most, they cited "investment of time into treatment, including visits to hospitals" (61 percent).

Read full story: bit.ly/FabryInsurance

Blood periostin may be key marker for kidney damage

By Andrea Lobo, PhD
FabryDiseaseNews.com

(June 2, 2023) Periostin, a protein associated with kidney injury, may be a valuable biomarker of Fabry disease's related kidney damage, according to new a study in Turkey.

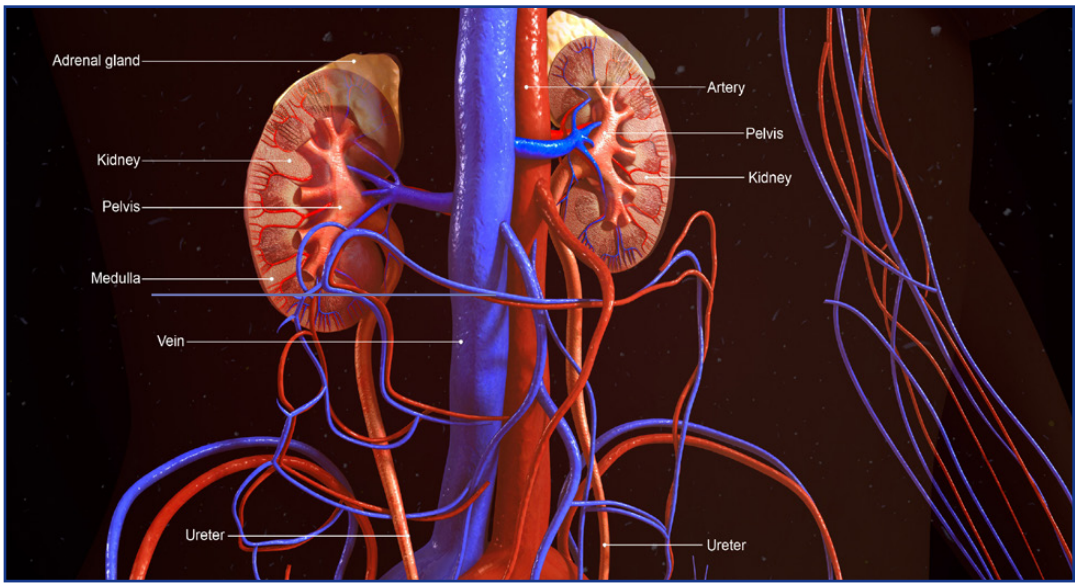
Researchers found that blood levels of periostin were correlated to proteinuria—the presence of proteins in the urine—which is one of the most critical indicators of kidney failure progression.

"In addition to standard ERTs [enzyme replacement therapies], periostin-reducing therapies may contribute to better kidney survival in Fabry disease," the researchers wrote.

The study, "Is just enzyme replacement therapy enough for Fabry disease treatment? Have we missed a trick?," was published in the journal *Nefrología* (English Edition).

Researchers sought to analyze the relationship between periostin and kidney damage in Fabry disease. Periostin levels previously were found to be elevated in people with other kidney disorders, and the protein is thought to mediate kidney inflammation and scarring.

Read full story: bit.ly/Periostin



Study: Alpha-synuclein clumps contribute to kidney cell damage

By Marisa Wexler, MS
FabryDiseaseNews.com

(May 19, 2023) In Fabry disease, a protein called alpha-synuclein forms clumps inside kidney cells, a toxic buildup that isn't reversed by conventional treatments.

Reducing that buildup can reverse cell damage, opening potential avenues for new treatment strategies, according to "Synuclein [alpha] accumulation mediates podocyte injury in Fabry nephropathy," which was published in The Journal of *Clinical Investigation*.

In untreated Fabry, podocytes showed the toxic Gb3 buildup along with signs of cellular damage. In biopsies from patients on ERT, Gb3 levels were reduced, but there was no clear reduction in other signs of cellular damage.

Using gene editing techniques, the researchers created a GLA-deficient podocyte cell line. In line with the biopsy findings, these cells exhibited Gb3 accumulation and signs of damage, including enlargement of lysosomes (the cellular "recycling centers" where Gal A is normally active). ERT treatment partially reversed the abnormal increase in lysosomal number and size, but didn't modify oxidative stress—when toxic molecules called reactive oxygen species outweigh the body's antioxidant defenses. The researchers conducted a series of transcriptomic and proteomic analyses.

Read full story: bit.ly/Alpha-Synuclein

Impairment in nerves that regulate heartbeat common in Fabry disease

By Marisa Wexler, MS
FabryDiseaseNews.com

(March 2, 2023) People with Fabry disease often have impairment in the nerves that help regulate heartbeat, which may serve as a prognostic measure to assess heart problems in the disease, a study reports.

Mild problems with heart nerves were found in many patients in the disease's earlier stages who didn't have notable heart health problems. More substantial nerve issues were only seen in those who already had fairly advanced Fabry disease and heart fibrosis (scarring).

The study, "Detection of sympathetic denervation defects in Fabry disease by hybrid [11C]meta-hydroxyephedrine positron emission tomography and cardiac magnetic resonance," was published in the *Journal of Nuclear Cardiology*.

The researchers used a new imaging technique to assess sympathetic denervation in people with Fabry disease. The technique combines magnetic resonance imaging (MRI) with positron emission tomography (PET) and uses a chemical tracer called [11C] meta-hydroxyephedrine to detect areas of denervation, or specific regions in the heart where there was a loss of nerve supply.

The hearts of 14 people with Fabry disease, aged 19-66, were imaged.

Read full story: bit.ly/FabryNerves

Same mutation caused late-onset and classic Fabry in same family

Case report findings show importance of individualized treatment

By Marisa Wexler, MS
FabryDiseaseNews.com

(March 24, 2023) The same mutation caused both late-onset and classic forms of Fabry disease among different members of the same family, according to a new report.

"To our knowledge, there are no previous reports showing that the same missense mutation causes both late-onset and classic form of [Fabry disease] in male carriers of the same family," the researchers wrote.

The team said these findings highlight the importance of individualized treatment—even for Fabry patients from the same family with the same disease-causing mutation.

In this report, scientists described the case of a Finnish woman who, as part of her participation in a separate study, was found to harbor a mutation in the GLA gene. The specific mutation, referred to as T410A, had been documented only twice before in scientific literature, having been found previously in families in China and Taiwan.

T410A is known as a missense mutation, meaning it causes a change in a single amino acid (the building blocks of proteins) when the GLA gene is read to produce protein. Structural analyses suggested this mutation would disrupt the structure of the GLA protein.

After the mutation was identified in the woman, many of her biological relatives also underwent genetic testing to see if they carried the mutation. Four of her siblings who were available for testing did not have the mutation, which suggests it probably developed de novo—meaning the mutation occurred for the first time in this patient, rather than being inherited from her biological parents.

The same mutation also was found in the woman's son, as well as his daughter (the original patient's granddaughter) and her two sons (the original patient's great-grandsons).

The woman, her son, and granddaughter all presented with symptoms consistent with late-onset Fabry. None of these individuals had substantial symptoms in early life, though all of them had cardiomyopathy (heart disease) in latter decades.

The two great-grandsons, however, had manifestations of classic Fabry disease. Both boys began to experience symptoms including abnormal fatigue and pain due to nerve damage when they were preschool age. One of the boys also had digestive symptoms.

"In the present family study, we showed that [the T410A mutation] causes classic FD [Fabry disease] in two young males and late-onset FD with cardiomyopathy in a middle-aged male, which, to our knowledge, is a novel finding," the researchers concluded.

Molecular analyses suggested that the two boys had essentially no alpha-galactosidase A enzyme activity, whereas their grandfather had some residual activity of the enzyme. This difference likely contributed to the more severe symptoms in the boys, the researchers said.

Treatment with enzyme replacement therapy was effective for easing the symptoms of the two young boys, the scientists reported. Their grandfather also was treated with enzyme replacement, though he ultimately died from heart complications. This case highlights a need for future studies to better determine risk of heart-related death in Fabry disease, the researchers said.

Read full story:
bit.ly/FabryMutation

Fabry disease still underdiagnosed, especially female

By Patricia Inácio, PhD
FabryDiseaseNews.com

(May 5, 2023) Fabry disease remains widely underdiagnosed, especially among women, according to a new population-based study that identified one undiagnosed case per every 3,225 people.

The study found that the genetic mutations that cause Fabry, a rare disorder primarily affecting the heart, nervous system, and kidneys, are more common than previously reported.

Still, the scientists noted that their estimate itself is likely an underestimation, given the strict criteria they used to consider a mutation as disease-causing. In addition, already-diagnosed patients were excluded from their analysis, and some mutation types were not part of the database they used.

"This study confirms that Fabry disease is more common than previously recognized and still underdiagnosed especially in women," the researchers wrote, adding that their findings "reflect that many women with Fabry disease are undiagnosed but still have the risks of kidney failure, heart disease, and stroke."

The study, "Population frequency of undiagnosed Fabry disease in the general population," was published in the journal *Kidney International Reports.*

A team of researchers at the University of Melbourne, Australia, sought to assess the frequency of Fabry in the general population. They found 100 GLA genetic variants among 119,329 individuals, with 99 classified as missense mutations.

Read full story:
bit.ly/FabryUnderdiagnosed

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Over half of adults with Fabry at risk of cardiac events

By Steve Bryson, PhD
FabryDiseaseNews.com

(May 12, 2023) More than half of adults with Fabry disease were found to have heart involvement that put them at risk for cardiac events—here, primarily associated with irregular heartbeat and heart failure, according to a new MRI study.

While an enlarged heart muscle and scar tissue formation were associated with worse cardiac events, the strongest predictor was the thickness of the muscle on the left side of the heart.

"Our study contributes to the evidence that [MRI] can be used to identify patients at high risk of adverse cardiac events," the researchers wrote.

Among the individuals with Fabry in the study, 16.3% "reached at least one cardiac endpoint," the team noted. For 9.1%, that was heart failure, while atrial fibrillation, or an irregular heartbeat, affected 12.7% of participants. "Cardiac death (1.8%) [was] rare in our patient [group]," the team noted.

Titled "Clinical and CMR characteristics associated with cardiac events in patients with Fabry disease," the study was published in the *International Journal of Cardiology*.

Read full story: bit.ly/Periostin

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