FIN FABRY EXPERT MEETING 2024

April 19-20, 2024

Prague, CZ

Meeting report

Fabry International Network

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THE LATEST ON FABRY AND THE HEART - DR. ALEŠ LINHART

Dr. Linhart reviews the cardiac (heart) manifestations of Fabry disease. The Fabry heart can show varying symptoms including cardiac hypertrophy, fibrosis, heart failure, arrhythmias (atrial fib, bradycardia and AV blocks, ventricular arrhythmias), and valvular disease. Heart disease may start around age 12 in males with classic Fabry, however, there is a wide spectrum of the age of onset and severity of manifestations. Storage of GL3 is seen in the heart muscle tissue, which leads to thickening and scarring (fibrosis), and then the heart can't function properly.

In terms of cardiac evaluation, the first test is often ECG/EKG which measures heart rhythm/conduction disturbances. Extended monitoring can be recommended in the form of a Holter monitor or loop recorder.
Often at the same visit, the doctors will perform an echocardiogram which is an ultrasound of the heart, that can show structural differences in the heart, like heart wall thickness and functioning of the heart valves. Cardiac MRI is increasingly used because it has better resolution and can measure thickness precisely. In particular, contrast with galladium on cardiac MRI can reveal scarred heart tissue (which leads to a higher risk of arrhythmias) which are not visible on echocardiogram; this may help determine the treatment plan in otherwise asymptomatic patients.

Studies have shown that Fabry-specific treatment, like enzyme replacement therapy or chaperone therapy, can stabilize heart disease in most cases. However, earlier treatment is recommended to prevent heart disease from developing. This adds to the conversation about when to initiate treatment, which is still complicated by classic vs late-onset phenotype, and male/female disease presentations.

STANDARD OF CARE - DR. UMA RAMASWAMI

Dr. Ramaswami reviews the concept of holistic patient-centered care. While healthcare providers have historically focused on objective measures of Fabry disease like lab tests, kidney function, and heart disease, there is also a need for more subjective patient-reported measures to capture the whole experience of living with Fabry disease. These may include questionnaires about quality of life, mental well-being, anxiety or depression, pain experience, and other standardized scales. It is imperative not only to collect these for data purposes but also to review the answers with patients to assess for unmet needs. Patients are more likely to seek help for mental health concerns when specifically addressed by their treating Fabry doctor (more than friends or family members).

In addition, it is important to recognize that a person's Fabry disease impacts life outside the doctor's office and yearly or twice-yearly visits. During COVID, Dr. Ramaswami's practice transitioned to a hybrid module with in-person visits annually and a virtual visit 6 months later. This hybrid practice also included a pilot study of the "Fabry App" where patients could track their symptoms over time to identify and discuss trends with their healthcare team. By increasing the volume of the patient voice in clinical care with frequent engagement and shared decision-making, patients report feeling more empowered to manage their Fabry disease.

PROMS AND PREMS IN FABRY DISEASE - DR. BOJAN VUJKOVAC

Dr. Vujkovac reviews the concepts of PROMs (patient-reported outcome measures) and PREMS (patient-reported experience measures).

- PROMs are standardized tools, originally developed for use in research, particularly in trials assessing the effectiveness of treatments. They can be generic (eg. depression scale) and applicable for a large patient group or targeted to a specific disease (eg. Fabry Pain Questionnaire).

- PREMs are also standardized tools, developed to study the patient experience. Patients' perceptions of their health and experience are key to providing excellent patient-centered care. These tools can be focused on relationships with healthcare providers (relational) or more practical accessibility experiences (functional). There are no published studies on PREMs in Fabry disease at the time of this presentation.

PROMs and PREMs can be used to help identify and assess unmet patient needs and define outcomes that are meaningful to patients. The US Food and Drug Administration and the European Medical Association have recently issued recommendations for the use of PROs and PROMs as secondary endpoints in drug approval process.

With Fabry disease in particular, these tools may allow providers to focus on patient quality of life, optimization of pain management, and management of GI symptoms. It will be important to consider that some symptoms will inevitably get worse with age when interpreting PROMs and PREMs over time. Dr. Vujkovac leaves us with the advice that providers should not only collect this data but also review it with patients and react to unmet needs.

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FABRY FEMALES: WHAT IS THE SAME AS MALES & WHAT'S NOT
DR. ROBERT HOPKIN

Dr. Hopkin begins by summarizing the history of Fabry females. Fabry disease is caused by mutations (pathogenic variants) in the GLA gene which is located on the X chromosome. While males have one X chromosome and Y chromosome (and therefore one GLA gene), females have two X chromosomes (and therefore two GLA genes). We used to think that women would be perfectly healthy with one working copy of the gene, but women were studied and found to have signs and symptoms of Fabry disease. Now we know that females with GLA mutations can develop a wide spectrum of symptoms of Fabry disease and may require treatment while others (25-30%) may remain without symptoms.

Overall, women are NOT carriers of Fabry disease, they are variably affected with Fabry disease. Of women with "classic" Fabry disease, 70% reported having symptoms across multiple studies. In fact, the risk for a woman with classic Fabry disease to have a serious medical event is higher than the risk for a "late-onset" male. The medical community's understanding of late-onset Fabry disease is less developed but we do know that individuals of both sexes are at risk of developing all symptoms. Women have enough risk to necessitate routine monitoring with treatment necessary if there is evidence of disease progression.

Dr. Hopkin provides an overview of what we know about symptoms and organ systems involvement in classic males vs. females with Fabry disease. Of note, both sexes have reported symptoms as young as age 2. Overall, he recommends that providers pay attention to the way they are framing their questions when asking about symptoms allowing for more than a simple yes/no response. He closes noting the limitations of the research performed thus far in pregnant and menopausal women with Fabry, with hopes for more in the future.

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WHAT WE DON'T KNOW ABOUT FABRY YET - DR. ALBERTO ORTIZ

Dr. Ortiz reviews that despite the extensive research, there remain limitations of our understanding of how to best treat Fabry disease. He identifies three unanswered questions:

Which individuals with Fabry disease need treatment, and when to start?

Many studies focus on classically-affected males, and therefore the greatest body of evidence for when to start treatment in this population. It becomes more difficult to make that determination in families with later-onset disease as well as in females due to variable expression of symptoms. Therefore, we often wait until women or late-onset individuals are showing signs of Fabry disease before they are treated. However, "what we see depends mainly on what we look for" meaning that more detailed testing of disease progression before symptoms occur can help us to determine who needs treatment. The aim is to prevent disease instead of treating full-blown disease.

How can we accelerate the clearance of glycolipid storage?

Enzyme replacement therapy works to clear the storage of glycolipids, but it takes time, up to 10 years to clear GL-3 storage. It might be possible to use other medications for the heart or kidneys to improve clearance. There is also the possibility that GCS inhibitors could be used at the beginning of a treatment regimen to facilitate a more rapid clearance of storage. More research is needed.

How can we address anti-drug antibodies (ADAs)?

Individuals with Fabry disease who make zero enzyme (CRIM negative) are known to be at an increased risk of developing anti-drug antibodies. If we can predict who is at risk, should we be doing anything differently to prevent the development of ADAs? In a different lysosomal storage disorder, Pompe disease, those with zero enzyme receive immune modulation when they first start enzyme replacement therapy to avoid ADAs. Perhaps a similar regimen could be studied in individuals with Fabry disease.

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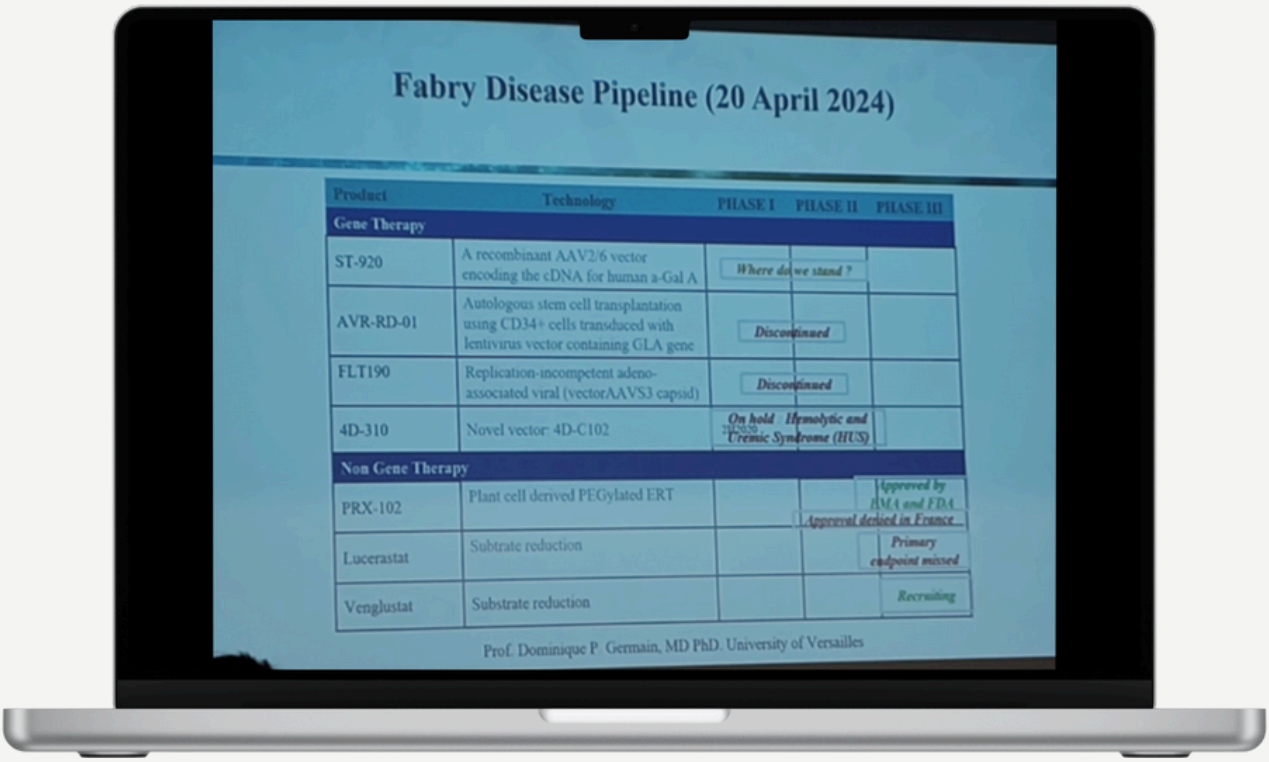
CLINICAL TRIALS UPDATE SUMMARY - PROF DOMINIQUE GERMAIN

Summary slide



MENTAL HEALTH, TRANSITIONING TO ADULTHOOD AND THE FABRY FOG
DR. NADIA ALI

Dr. Ali begins by summarizing two recent studies presented as posters at the American College of Medical Genetic 2024 meeting.

The first, titled "Cognitive and mental health challenges in Fabry disease: a real-world evidence study using social media" showed that depression was the most common mental health concern in Fabry patients, followed by anxiety and then ADHD.

The next, titled "Mental health in Fabry disease: results from a North American survey of 401 participants" showed that anxiety/stress was the most common mental health concern followed by depression and Fabry fog. Notably, 80% of participants said that mental health was as important as physical health in the management of Fabry disease. Patients reported that the person most likely to get them to seek mental health care is their Fabry doctor (more so than nurses, teachers, family members, etc).

Dr. Ali reviews what is known about "Fabry fog" that is reported by some patients. The Mroczek 2022 article summarizes conflicting reports that suggests 0-30% of adults with Fabry show cognitive difficulties, usually in executive functioning, information processing speed, and attention. In addition, things that are common with Fabry can affect cognitive functioning such as stroke, anxiety, depression, insomnia, and medications. Emory is conducting a study with neurocognitive testing in adults, results not yet available.

Managing stress (disease-related or otherwise) is important for mental health and overall wellbeing. Dr. Ali recommends having an "early warning system" by learning to identify your stress behaviors. She also recommends building an individualized tool box of self-care activities, peer support, therapy, prompts to challenge negative thoughts, and anything else that makes you feel empowered.

Finally, Dr. Ali discusses transitioning to adulthood in the healthcare and home setting. This may start with an older child beginning to take over responsibility for one or two aspects of their care, like confirming appointments or taking pre-medication as instructed. Ultimately, the goal is for the emerging adult to transition to understanding their own disease, managing their evaluations and treatment, and family planning. Dr. Ali has the following tips to share:

- Don't change everything at once, start with small steps.
- Establish care with your new Fabry doctor before health problems come up.
- Compile a list of doctors' contact information.
- Make a written list of your questions before each visit and WRITE DOWN what you talk about at your visit.

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Meeting report by Casey McKenna, MS, CGC

Empowering people living with Fabry

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