The Virtual 2021 Family Conference and Scientific Symposium brought the leukodystrophy community together again this year!

Due to the ongoing pandemic, the Family Conference and Scientific Symposium were held virtually. While we are sad that we were not able to meet in person, we were still blown away by the support of the community – families, medical professionals, advocates and allies – allowing us to Grow Together despite the distance.

In 2020, we opted to cancel the Scientific Symposium to focus as much time on the leukodystrophy families as possible. We brought the Symposium back in 2021 to provide the research community an opportunity to discuss their progress since the last time the group met in 2019. The summaries of those talks are featured in part in this newsletter, and the remaining summaries will be included in the November newsletter.

We focused a lot of energy in our type-specific sessions this year for the Family Conference. It is an annual effort to share information on as many leukodystrophies as we can and celebrate the advances that are being made in the field to benefit everyone affected by a leukodystrophy. We were thrilled to partner with Cure MLD and the Calliope Joy Foundation, KrabbeConnect, and the Vanishing White Matter Consortium to offer expanded type-specific content for the MLD, Krabbe, and VWM communities. We recorded the sessions, and they are available to view on our YouTube channel. Search for “ULF Office” to go to our page and view all of the videos available, or search for the “2021 ULF Virtual Conference” playlist to view just the videos from this year’s meeting.

We have every intention of hosting an in-person conference next year!

### Conference By the Numbers

- 25 Countries Represented
- 40 US States Represented
- Over 30 types of leukodystrophies represented

### Save the Date

**JUNE 23 - 25, 2022**

EAGLEWOOD RESORT AND SPA
1401 NORDIC ROAD, ITASCA, IL 60143
Dear Friends and Supporters of the United Leukodystrophy Foundation,

Wow, the summer is flying by too fast. We have again hosted a very successful family and scientific conference this year. Over 400 of you attended! I hope each of you got the information you needed to help you through your journey with leukodystrophy. The virtual format has allowed us to reach patients in 25 countries, 40 states, and 28 different kinds of leukodystrophy. Make sure to watch the videos posted on our website. One of the comments I have heard is that we need to be in-person again. This is the one component of our conference that has been missing the past two years. For those who have never been to our in-person conference, you have missed the most valuable part of the experience. We look forward to seeing all of you next year in person.

The ULF is working on many projects that will benefit all of you in the future. Please keep an eye on our website and our social media so you can keep informed on the work we are doing for your benefit. We have been working with other leukodystrophy patient advocacy groups (PAGS) to find ways that we can collaborate for the benefit of all of us affected by leukodystrophy. Our ambassador program is moving forward, and many of you will be asked to be a part of that program in the future.

We want to thank all of you for your financial support of the ULF. We cannot accomplish all we do without your support. We are so excited to have Chris Rice as our new executive director, who will help us become an even more effective organization, assisting everyone affected by leukodystrophy. Please encourage him in his work as he leads us forward.

As I close, I want you to know that I am thinking of all of you who have just been diagnosed with leukodystrophy, and I have a special prayer for those who have lost a loved one to this disease. Do your best to stay healthy, and we look forward to seeing you in Chicago next June.

ROBERT RAUNER
ULF Board President
BACKGROUND
Although the literature suggests that men are affected earlier and more severely than women, the natural history of specific symptoms, from the perspective of the individual with AMN, and the effectiveness of their treatment has not been well described.

SPECIFIC AIMS OF STUDY
• To delineate in detail the natural history of symptoms of AMN in men and women
• To explore the psychological, social and quality of life implications of impairment related to symptoms of AMN
• To apply the knowledge gained from this study to improving clinical protocols and multidisciplinary care for men and women with AMN

RESULTS
Participants
• 84 men and 214 women completed the survey
• Women with AMN completing survey were older than men
• Women more likely to be diagnosed due to family history instead of symptoms compared to men
• Men were more likely to be single, never married than women

Neurology
• Top 5 symptoms: Spasticity / stiffness in legs, Weakness in legs, Change in gait, Loss of sense of where feet are in space, Numbness / tingling in feet
• Women were more likely to have pain and burning in their feet than men
• Men were more likely to: Have experienced falls, Need assistance with walking and to have experienced gait changes earlier than women, Have hearing loss
• Sleep disturbance was very common including Restless Leg Syndrome, Excessive Daytime Sleepiness and Trouble falling asleep
• Cognitive changes common in both men and women with AMN (without cerebral form). Men and women experiencing change in cognitive abilities:
  • More likely to have sleep problems
  • More likely to rate their overall health as poor

Endocrinology
• Diagnosed with adrenal insufficiency / Addison's --- Men 62.2% vs. women 2.7%
• Hypothyroidism more common in women than men with AMN and more common than the general USA population
• Hair loss was more common in men than women and occurred at an earlier age with 52% of men experiencing hair loss before age 30 and only 8% of women

Bowel Concerns
• Common and included: Urgent need to pass stool, Constipation, Bowel incontinence

Bladder Concerns
• Very common including: Urgent need to pass urine, Frequent need to void, Trouble emptying bladder, Urinary incontinence, Awaken at night to urinate
• Catheters were used more commonly by men (23.8%) than women (6.5%)
• Erectile dysfunction / difficulties with sexual function were present in 78.1% of men with AMN

Quality of Life
• Men and women who rated overall health as poor (0-4 out of 10) have: More neurological symptoms, More likely to have a change in cognitive abilities, More sleep problems, More bowel symptoms, More bladder symptoms
• Overall, those with depression / anxiety were more likely to rate health as poor (0-4) and to have sleep disturbance

SUMMARY
Although the medical literature focuses primarily on the neurological symptoms of AMN, quality of life is determined by multiple factors including severity and natural course of not only the neurological symptoms but also of endocrine, GI and urology symptoms.

Depression / anxiety and sleep disturbance are common and need to be addressed as part of multidisciplinary care for AMN.
LERIGLITAZONE IMPROVED PROGRESSION OF MYELOPATHY-RELATED SYMPTOMS, AND REDUCED CEREBRAL LESIONS IN PATIENTS WITH ADRENOMYELONEUROPATHY IN A PHASE 2/3 CLINICAL STUDY

BY: WOLFGANG KOEHLER, MD FOR ADVANCE STUDY GROUP*, UNIVERSITY OF LEIPZIG MEDICAL CENTER

Leriglitazone was studied by an International Group of researchers from the EU and US in a 2-year placebo-controlled clinical trial in adult male patients. Our objective was to study the efficacy of leriglitazone on the progression of adrenomyeloneuropathy (AMN).

As a primary endpoint of the study, the 6-minute walk test (6MWT) was used. Secondary endpoints were measures to test body sway amplitude and balance, measures to test the severity of myelopathy and other neurological symptoms as well as patient reported outcomes, MRI, and plasma biomarkers such as neurofilament light (NfL).

116 patients were randomized (77 leriglitazone, 39 placebo). 96 patients completed double-blind treatment. Results show some beneficial effects in favor for leriglitazone treated patients; however, the primary endpoint (6MWT) was not met. In more detail, we saw clinically meaningful effects on walking disability (6MWT) and EDSS ambulation in early-stage patients. Clinically meaningful differences could be observed in various sway parameters and conditions, leading to favorable trends in clinical scales, quality of life, and global impressions.

Most interestingly, we observed a decrease in incidence of cerebral lesion progression aligned across radiological, clinical, and biomarker-based observations. Only patients in the placebo arm developed clinically progressive cerebral ALD.

The most frequently reported adverse events were edema and weight gain; however, treatment discontinuation rate for adverse events was low (10.4% leriglitazone vs. 5.1% placebo).

In conclusion, leriglitazone had a favorable safety profile, improved postural control, and reduced the development of cerebral lesions.

*ADVANCE Study Group:
- US: Baltimore (Ali Fatemi), Boston (Reza Seyedsadjadi, Florian Eichler), Stanford (Jacinda Sampson, Keith van Haren, Sarada Sakamuri)
- EU: Germany (coordinator, Wolfgang Koehler, Astrid Unterlauft), France (Fanny Mochel), Hungary (Judith Molnar), Italy (Ettore Salsano), Netherlands (Marc Engelen), Spain (Josep Gamez), United Kingdom (Robin Lachman)
- Minoryx (Marc Martinell, Uwe Meya, María Pascual, Adriana Mantilla, Silvia Pascua, Anna Vila, Maria Rovira, Guillem Pina)

Contact: Wolfgang.Koehler@medizin.uni-leipzig.de
ANTISENSE THERAPY IN A NEW RAT MODEL OF ALEXANDER DISEASE

BY: TRACY L. HAGEMANN, PHD, W AISMAN CENTER, UNIVERSITY OF WISCONSIN – MADISON

Alexander disease (AxD) is a rare neurodegenerative disorder caused by mutations in the gene for glial fibrillary acidic protein (GFAP), a structural protein in cells called astrocytes in the brain and spinal cord. To study the effects of GFAP mutation on astrocytes and other cell types in the central nervous system (CNS), we have generated a new rat model by mutating the rat Gfap gene to mimic the same mutations identified in patients with the disease. The AxD model rat achieves normal developmental milestones but fails to thrive after weaning, and about 14% die of unknown cause between 6 to 12 weeks of age. Young adult animals are small, gaunt, and motor-impaired with an abnormal gait. In addition, they exhibit all the pathological hallmarks of AxD including GFAP accumulation and aggregation, increased expression of stress response proteins, and white matter deficits in spinal cord. This makes them well suited as a model in which to test new therapies for improvement in molecular and cellular pathology as well as functional behavior. We show that treatment of the rat model with antisense oligonucleotides, small pieces of DNA designed to target the messenger RNA encoding GFAP protein, prevents disease when administered at an early age and reverses pathology and motor deficits even when delivered at late stages of disease. The rat model provides an important new tool to study disease mechanisms in AxD, including the effects of astrocyte dysfunction on myelination in the CNS, and a pre-clinical model with measurable behavior deficits to assess functional improvement with new therapies.

CAUSES AND CONSEQUENCES OF DISTURBED BRAIN ION AND WATER HOMEOSTASIS IN THE LEUKODYSTROPHY MLC

BY: DR. ROGIER MIN, PHD, AMSTERDAM UMC

Dr. Min presented some recent results concerning Megalencephalic Leukoencephalopathy with subcortical Cysts (MLC). Astrocytes, important supportive brain cells, are primarily affected in this disease. In his talk, Dr. Min highlighted work from the lab demonstrating that the balancing of potassium in the brain is disrupted in MLC mice. When the brain is electrically active, potassium accumulates in the fluid surrounding brain cells. If potassium levels are not quickly returned to normal, this can trigger excessive electrical activity and epileptic seizures. Astrocytes have the ability to quickly remove excess potassium and prevent dangerous accumulation. In MLC, the ability of astrocytes to remove potassium is compromised, leading to a higher seizure susceptibility in MLC mice and a high prevalence of seizures in MLC patients. By studying the molecular defects that cause this compromised astrocyte function, the lab hopes to find ways to repair astrocyte function in MLC.

DIAGNOSTIC CHALLENGES IN ADULT GENETIC LEUKOENCEPHALOPATHIES AND GENETIC MIMICKERS OF ACQUIRED MYELIN DISORDERS

BY: ROBERTA LA PIANA, MD, PHD, MCGILL UNIVERSITY

Genetic leukoencephalopathies are considered rare in the adult population. However, several lines of evidence suggest that there is a larger than expected number of adult patients with genetic leukoencephalopathies who are currently not diagnosed. We applied an integrated approach which combines the identification of neuroradiological patterns with the analysis of next-generation genetic sequencing data.

Our work led to the description of a cohort of 72 adult subjects with leukoencephalopathy of probable genetic origin and we discovered the genetic cause of their diseases in 36.1% of them. The overlapping with acquired white matter diseases such as multiple sclerosis or vascular white matter disorders represent a major challenge in the diagnostic process.
We invite you to join the HOME Study, a Natural History Of Metachromatic Leukodystrophy, an initiative that expands patient and caregiver engagement in clinical research. Developed by the National Organization for Rare Disorders (NORD®), in partnership with the FDA, to collect data that will help to support clinical trials and accelerate regulatory approvals for metachromatic leukodystrophy (MLD), the HOME Study was designed for you and your loved ones to contribute to research from the comfort and safety of your home, without the demands and challenges of traveling to a study site.

WHO CAN JOIN THE STUDY?
This study is offered in English and open to anyone who has a confirmed diagnosis of metachromatic leukodystrophy.

WHAT IS THE STUDY SCHEDULE?
This is a 12-month study with five 1-hour virtual visits that can be scheduled at your convenience. Virtual study visits include a baseline meeting, and then scheduled virtual meetings at three, six, nine, and twelve months after study enrollment.

The first step is to register at mldhomestudy.iamrare.org and consent to participate in the study. Then our study coordinator will contact you to provide a welcome packet and schedule some time to meet with you!

HOW WILL DATA BE COLLECTED?
Study participants will receive a complimentary tablet to support their engagement in the study. Data will be collected through online survey questions, virtual video-based study visits, and an optional mobile application.

TO LEARN ABOUT AND JOIN THE HOME STUDY, VISIT:
rarediseases.org/ mld-homestudy
bit.ly/HOMEStudy

CONTACT THE HOME STUDY TEAM
MLD@rarediseases.org

LEARN MORE ABOUT NORD
rarediseases.org
We’ve launched a Data Collection Program!

The Yaya Foundation, in collaboration with an innovative non-profit called RARE-X, has launched a data collection program, sometimes called a patient registry, that will get our community’s data onto the best-in-class rare disease data collection portal of the Broad Institute of MIT and Harvard and ultimately to researchers, clinicians, and drug developers across the globe.

The launch of a data collection is an important milestone for us and was a key priority laid out in our Research Roadmap. This research will help accelerate diagnosis of 4H, improve understanding of the disease, and support efforts to discover therapies that will help people affected by 4H live longer, better lives.

In 3 short weeks since launch, 30 families from 8 different countries have enrolled in the data collection program. Given the size of the 4H patient population, this is already a meaningful cohort! Also of note, more than one third of the families who have registered are from outside the United States, which speaks to the global impact that The Yaya Foundation is making.

“A lot of people in our group have been waiting for this!”

–Mother of child affected by 4H

Thank you for your support and for celebrating this milestone with us,

The Yaya Foundation for 4H Leukocystrophy

Stay tuned and follow our website, Facebook, LinkedIn and Twitter for more milestones we’re achieving!
ULF FACE MASKS

For a $15 donation, we will send you an adult-size ULF branded face mask! The masks are made in the USA, and have a 100% cotton inner liner with a 100% poly outer shell. They are machine washable. Please use your best judgment for your health in taking the proper precautions to avoid risks against illness, disease, or other circumstances.

TO ORDER YOUR MASK, VISIT ULF.ORG/MASKS

UNLOCK

CEREBROTENDINOUS XANTHOMATOSIS
An initiative of the United Leukodystrophy Foundation

Join a virtual Patient-Focused Drug Development meeting dedicated to CTX on September 14, 2021

Learn how you can participate at ctxresource.org/unlockctx