Alex TLC Research Summary
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Research summary of recent leukodystrophy research and clinical trials, includes article summaries and direct links to websites and articles.

Clinical trial updates

Adrenoleukodystrophy (ALD)

Leriglitazone has met the primary endpoint in NEXUS, the pivotal trial for pediatric patients with cerebral Adrenoleukodystrophy

https://www.minoryx.com/media/leriglitazone_has_met_the_primary_endpoint_in_nexus/

We would like to share some really exciting news about the results of the Nexus trial which Minoryx Therapeutics has just released. The Nexus trial which has recently completed, was a clinical trial to show the efficacy of leriglitazone in young boys with early stage cerebral adrenoleukodystrophy.

Research summaries

Adrenoleukodystrophy (ALD) and Adrenomyeloneuropathy (AMN)

Practical Approach to Longitudinal Neurologic Care of Adults With X-Linked Adrenoleukodystrophy and Adrenomyeloneuropathy

https://pmc.ncbi.nlm.nih.gov/articles/PMC11450743/

Adrenoleukodystrophy (ALD) and adrenomyeloneuropathy (AMN) are X-linked genetic disorders with significant lifelong implications. ALD primarily affects men, but women can also develop debilitating symptoms, including progressive neuropathy and myelopathy, though adrenal insufficiency and cerebral demyelination are rare. Early identification of symptoms and establishment of care with a neurologist are essential for lifelong management and surveillance. Importantly, women with ALD should not be assumed asymptomatic, as many experience pain and mobility challenges that require intervention. Currently, disease-modifying therapies are limited to cerebral ALD (CALD) in children. Hematopoietic stem cell transplantation (HSCT) can halt disease progression in early-stage CALD, as of recently adult males may now be eligible with strict criteria in place. Gene therapy and PPAR-γ agonists like leriglitazone, are under investigation for AMN and CALD as novel therapies and while promising, these treatments are not yet approved for adults. Challenges in managing ALD/AMN include addressing emotional burdens, such as caregiver stress and genetic guilt, and improving access to specialised care. Women, often caregivers themselves, may deprioritise their own health, necessitating targeted mental health support. Future research is critical to understanding adult ALD/AMN, including biomarkers and advanced imaging techniques for improved risk stratification and treatment outcomes. Developing disease-specific interventions and expanding therapeutic options will enhance the quality of life for affected individuals. Additionally,

neurologists must remain knowledgeable of emerging therapies and clinical trials to offer comprehensive, multidisciplinary care.

Adrenoleukodystrophy (ALD), Metachromatic Leukodystrophy (MLD), Krabbe Disease

Emerging Role of Ubiquitin Proteasome System and Autophagy in Pediatric Demyelinating Leukodystrophies and Therapeutic Opportunity

https://www.mdpi.com/2073-4409/13/22/1873

In the cell, when a protein is misfolded (not folded correctly) and does not pass the quality check, it is sent for degradation (break down) through two different processes that breakdown and recycle damaged or nonfunctional proteins, autophagy and the Ubiquitin Proteasome System (UPS). However, these degradation systems can become dysregulated and lead to the accumulation of abnormal proteins, subsequently inducing cellular toxicity and pathology onset. While the exact molecular mechanisms underlying demyelinating leukodystrophies remain unclear, the involvement of autophagy and UPS was suggested and data summarised in this review. Studies reported decreased levels of autophagy markers in the brain tissue of individuals with X-linked adrenoleukodystrophy (X-ALD), suggesting compromised autophagic processes. The potential involvement of impaired autophagy and UPS in the demyelination observed in globoid cell leukodystrophy (GLD) also known as Krabbe Disease was strengthened by the study of the twitcher mouse model which is a mouse that naturally has a similar mutation to Krabbe and is therefore a good disease model to study the disease. Next, researchers investigated the potential of autophagy modulators on cellular and mouse disease models. They showed that targeting autophagy in a mouse model of X-ALD using an mTOR inhibitor (group of drugs that inhibit the mammalian target of rapamycin [mTOR]), temsirolimus, could restore autophagic activity. In twitcher mice, treatment with the mTOR inhibitor rapamycin decreased the amount of protein aggregates within cells. While showing some potential, these treatments also showed limited efficacy. Additional studies are necessary to further investigate and optimise these interventions.

GM2 Gangliosidosis

4-Phenylbutyric acid mitigates ER stress-induced neurodegeneration in the spinal cords of a GM2 gangliosidosis mouse model

https://academic.oup.com/hmg/advance-article/doi/10.1093/hmg/ddae153/7889395

GM2 gangliosidosis is characterised by motor neuron loss and subsequent spinal cord dysfunction and neuromuscular deficits. What links the disease to cell loss remains unclear, but this research article focused on the potential role of endoplasmic reticulum (ER) stress. The ER is an intracellular compartment involved in protein folding which is where a protein is folded into a 3-dimensional structure and becomes functional. When a protein is not folded correctly or unfolds, it is not able to function correctly and misfolded proteins then build-up, and ER stress is triggered, activating the unfolded protein response (UPR) to tackle the issue. However, persistent ER stress and UPR activation can become detrimental by provoking programmed cell death, called apoptosis. Using a mouse model of GM2 gangliosidosis ($Hexb^{-/-}$), researchers studied the role of ER stress in disease progression. They then evaluated the therapeutic effect of orally administered sodium phenylbutyric acid (4-PBA), an ER stress modulator. Data showed that ER stress markers appeared early in disease

pathogenesis, at 60 days of age, and were accompanied by early apoptotic markers, rapidly progressing to severe cell loss. However, early 4-PBA treatment at 40 days of age resulted in decreased ER stress and apoptotic markers, as well as delayed neuromuscular impairment and increased life span. The fact that reducing ER stress benefited motor neuron survival in the context of GM2 gangliosidosis highlighted a pathway of interest for further investigations.

Leukodystrophy

Being the other child - A systematic review on the quality of life and mental health of siblings of children with rare diseases

https://www.sciencedirect.com/science/article/pii/S0891422224002002?via%3Dihub&utm_source=emailoctopus&utm_medium=email&utm_campaign=November%202024

This systematic review evaluated 37 finely selected studies that focused on the quality of life (QoL) and mental health of siblings of children with rare diseases. The eligibility criteria were met by 32 cross-sectional studies and 5 longitudinal studies. The included studies were from 12 countries spanning Europe, North America and Asia. QoL and mental health data came from either self-report, parent-reported data or both. This review revealed mixed findings, as some studies reported no difference while some showed greater impairment of QoL and mental health in siblings of children with rare diseases compared to norm data (data from the general population to have as a comparison). In longitudinal studies where study participants were followed for over two years, QoL and mental health scores showed improvement over time. The report further revealed that parental depressive symptoms, dysfunctional family dynamics and low family income can have a significant impacts on the quality of life and mental health of siblings. These observations were in line with previous research on siblings of children with chronic diseases. Disease-specific differences could not be established as only global rather than disease-specific QoL measurements were used. Nonetheless, this report highlighted the need for preventive interventions, that include the whole family system, regardless of diagnosis.

Implementing genomic medicine in clinical practice for adults with undiagnosed rare diseases

https://www.nature.com/articles/s41525-024-00449-1

Undiagnosed rare diseases continue to remain a global challenge, particularly in adults, leading to prolonged diagnostic journeys and significant health impacts. This study investigated 232 adults with suspected rare diseases using advanced genetic tools, including exome and genome sequencing. Among the participants, 66 individuals (28.4%) received a genetic diagnosis, while 12 were diagnosed with non-genetic conditions, such as autoimmune or infectious diseases. Neurological conditions, especially cerebellar ataxia and leukodystrophy, had higher diagnostic success rates. Advanced methods, such as copy-number variation analysis and screening for repeat expansions, further improved accuracy. This study also revealed that individuals whose symptoms began in childhood experienced longer diagnostic delays, typically due to the complexity of their cases and limited access to modern technologies in earlier years. However, reanalysis of genetic data over time helped increase diagnostic success as new discoveries emerged. Receiving a diagnosis enabled personalised care. For those with genetic conditions, tailored management strategies included reproductive counselling, family screenings, and drug repurposing, with notable improvements in

some patients. Similarly, individuals with non-genetic conditions benefited from specific treatments, such as immunotherapy, leading to symptom relief. This research highlights the power of genomic medicine in diagnosing challenging conditions and improving outcomes for adults with rare diseases. By combining multidisciplinary clinical evaluations and genetic technologies, healthcare systems can reduce diagnostic delays and enhance patient care. The findings emphasise the need for continued efforts to address undiagnosed cases, particularly for adults with childhood-onset symptoms.

POLR3-Related Leukodystrophy

Stress and Quality of Life of Parents of Children With POLR3-Related Leukodystrophy: A Cross-Sectional Pilot Study

https://pmc.ncbi.nlm.nih.gov/articles/PMC11590388/

Caring for children with POLR3-related leukodystrophy presents unique challenges due to the disease's progressive nature and evolving symptoms. This study assessed parental stress, quality of life, and their determinants in a cohort of parents, with findings revealing normal stress levels but significantly lower quality of life compared to normative samples. Approximately 80% of parents exhibited stress levels within the normal range, potentially attributed to an average of 11 years since diagnosis, which allowed families to adapt. Access to specialized Leukodystrophy Centers of Excellence and caregiving resources likely contributed to these results. However, clinically significant stress was linked to external life stressors, such as financial difficulties or personal health issues, rather than the child's clinical progression. Parents reported reduced quality of life, particularly due to worry about their child's health, societal perceptions, and the family's future. Despite this, family relationships remained strong, acting as a protective factor. Time since diagnosis was a significant predictor of increased maternal quality of life, likely reflecting adaptation over time. Perceived injustice negatively impacted quality of life, while adaptive coping strategies, such as open communication and active engagement with the child, positively influenced maternal well-being. Limitations included the small sample size, cross-sectional design, and exclusion of non-English/French speakers, which may have overlooked vulnerable populations. Future longitudinal and qualitative studies are recommended to understand the evolution of stress and quality of life and guide interventions. Early psychological, educational, and financial support for caregivers is essential to improving parental well-being and fostering resilience in families coping with this rare disease.

Concise Articles

Leukodystrophy

Affinia Therapeutics and Forge Biologics Announce AAV cGMP Manufacturing Partnership to Advance Affinia Therapeutics' Pipeline of Next-Generation Gene Therapies to the Clinic

https://www.forgebiologics.com/affinia-therapeutics-and-forge-biologics-announce-aav-cgmp-manufacturing-partnership-to-advance-affinia-therapeutics-pipeline-of-next-generation-gene-therapies-to-the-clinic/

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