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.

Adrenoleukodystrophy (ALD)

Abcd1 Deficiency Accelerates Cuprizone-Induced Oligodendrocyte Loss and Axonopathy in a Demyelinating Mouse Model of X-linked Adrenoleukodystrophy

https://actaneurocomms.biomedcentral.com/articles/10.1186/s40478-023-01595-w#Sec19

This article examines X-linked adrenoleukodystrophy (X-ALD) a disease that damages the myelin sheath surrounding the axons (nerve fibres). This mutation results in a deficiency of the adrenoleukodystrophy (ALD) protein which is responsible for the transportation of VLCFAs into peroxisomes so that they are broken down. Researchers conducted experiments with cuprizone, a copper chelator which is commonly used to study various diseases including multiple sclerosis. Cuprizone can cause damage to oligodendrocytes, a type of brain cell that maintains the myelin sheath, causing it to degrade and eventually lead to impaired communication between neurons. The mice were fed a cuprizone diet for up to 5 weeks and it was found that after 3 weeks of cuprizone exposure in the early phase, the *Abcd1*-deficient mice displayed a significant reduction in oligodendrocytes when compared to wild-type (wt) mice that do not have an ABCD1 mutation. These findings were parallel with the considerable scale of axonal damage in the *Abcd1*-deficient mice. Another study observed post-mortem cerebral ALD tissue specimens in which they found that there were enlarged lipid-saturated macrophages in the tissue which suggests that there is a connection between *Abcd1* deficiency and myelin clearance. This information will be important for developing new treatments for X-ALD in the context of demyelination.

Neurofilament light chain levels in cerebrospinal fluid as a sensitive biomarker for cerebral adrenoleukodystrophy

https://onlinelibrary.wiley.com/doi/full/10.1002/acn3.51818

Cerebral Adrenoleukodystrophy (CALD) is the advancement of adrenoleukodystrophy (ALD) and typically has a poor prognosis for patients. This research sets out to investigate if neurofilament light chain levels (cNfL) obtained from cerebral spinal fluid can be used to identify and grade the severity of CALD before and after treatment. This cross-sectional study was conducted using 41 male ALD patients whose cNfL and MRI-based Loes severity scores were measured. The study used patients with both CALD and adrenomyeloneuropathy (AMN). The results demonstrated that the CALD patients had higher cNfL levels in comparison to the AMN patients as expected. The results also concluded that the cNfL levels positively correlated with the Loes scores which is a grading system that assesses the severity of white matter brain lesions. The use of cNfL as a biomarker is also proven to be useful as patients who advanced from AMN to CALD had increasing levels of cNfL

throughout the study. On the other hand, patients who underwent hematopoietic stem cell transplantation (HSCT) experienced a period of rapidly decreasing cNfL throughout their treatment and the course of the study. From previous research, it has been proven that HSCT has a higher efficacy when administered at an earlier stage of the disease. This highlights the importance of developing diagnostic and prognostic techniques such as cNfL to detect CALD at an earlier stage to ensure more effective treatment results. However, while this study shows positive results it is important to take into account the very small sample size of 41 male ALD patients. In order to produce more reliable results of cNfL as a biomarker for CALD a much larger sample size of patients would be required for a longitudinal study.

Canavan Disease

Developing Hypoimmunogenic Human iPSC-Derived Oligodendrocyte Progenitor Cells as an Off-The-Shelf Cell Therapy for Myelin Disorders

https://onlinelibrary.wiley.com/doi/10.1002/advs.202206910Canavan disease is a rare yet lethal form of leukodystrophy which occurs as a result of a genetic mutation within the aspartoacylase (ASPA) gene. This gene acts as a metabolic enzyme which is concentrated in the brain. The deficiency of this gene leads to increased levels of the substrate N-acetyl-aspartate (NAA). At present, there are no approved therapies or treatments for the disease, and this research investigates a potential treatment for the future. The research proposes an “off the shelf” cell therapy using human induced pluripotent stem cells (iPSC) from a healthy donor modified to carry the wild type (non-mutated) ASPA gene through editing of the human leukocyte antigen (HLA) molecules to disrupt their expression and then differentiate those iPSCs into hypoimmunogenic oligodendrocyte progenitor cells (OPCs) that were then transplanted into mouse brains. Hypoimmunogenic cells were created as universally compatible cells to prevent an immune response from occurring. The OPCs survived well, matured into oligodendrocytes which were able to express the non-mutated ASPA gene and dramatically improved Canavan disease symptoms. NAA concentrations decreased, myelination and vacuolation (spongy degradation) improved as did motor functions in these mice. In addition to this the OPC cell therapy has been found to act as an effective aid to the absorption of medicine used to treat other metabolic brain disorders and can also be applied to other demyelinating disorders such as multiple sclerosis (MS). Overall, human iPSc-derived OPCs have been proven in this research to be a suitable candidate to treat Canavan disease. However, more research will need to be conducted to ensure the efficacy and prevention of donor rejection in all patients.

Leukoencephalopathy with calcification and cysts (LCC)

Leukoencephalopathy with calcification and cysts Labrune Syndrome: A Rare Leukodystrophy

https://www.cureus.com/articles/140761-labrune-syndrome-a-rare-leukodystrophy#!/

Labrune syndrome aka Leukoencephalopathy with calcification and cysts is a rare neurological condition characterized by progressive cerebral degeneration, typically displaying a strong genetic predisposition in families. The article reviews a case report of a 21-year-old male patient diagnosed with Labrune syndrome as he presented with seizures, abnormal cysts and calcium deposits in various parts of his brain. Due to the resemblance in the brain imaging and symptoms of Labrune syndrome with other diseases, such as hydatid disease and neurocysticercosis, it is a challenging condition to diagnose. Particularly, as in this case, the patient did not present any signs of the

disorder until he had experienced his first seizure in his 20s. However, Labrune syndrome displays a distinct imaging pattern therefore its diagnosis was further confirmed by numerous laboratory tests which ruled out the potential for other diseases Furthermore, it was determined through genetic testing that the disease was a result of a mutation in the SNORD118 gene which produces a ribonucleic acid (RNA) that is involved in the production of ribosomes which are protein producing machines in our cells. Therefore, a mutation in this gene will consequently disrupt the production of RNA, which is a crucial part of ribosome function. In the case of Labrune syndrome, researchers believe that this interference will result in brain degeneration as the change in RNA production will impact the normal function and communication of brain cells. Current treatment for Labrune syndrome focuses on managing the symptoms and surgery will be approved if the cysts cause a mass effect. Therefore, the authors of this article emphasize the significance of further studies to fully comprehend the disease's progression and establish effective therapies.

Vanishing White Matter Disease (VWM)

Adult-Onset White Matter Vanishing Disease With Ovarian Failure in a Salvadoran Patient

https://www.cureus.com/articles/157902-adult-onset-white-matter-vanishing-disease-with-ovarian-failure-in-a-salvadoran-patient#!/

This article refers to a unique case of leukodystrophy known as adult-onset vanishing white matter disease (VWMD) associated with ovarian failure. The condition can affect both children and adults underlying detrimental consequences on their neuronal and motor systems with symptoms ranging from mild to severe. In this case, a 35-year-old female patient was admitted to the hospital due to a two-year history of spastic gait, and cognitive impairments such as balance, forgetfulness and learning difficulties. During her examination, she described imbalanced menstrual cycles and an inability to conceive a pregnancy. Hormonal testing revealed an abnormal increase in the follicle-stimulating hormone (FSH) and estradiol levels indicating possible ovarian failure. Brain MRI showed white matter degeneration and signs of leukodystrophy. To confirm the diagnosis genetic testing was performed and revealed the presence of two pathogenic gene variants known to cause VWMD in adults. The patient was discharged, and current treatment is restricted to managing the symptoms. Through this article, a unique case of VWMD with ovarian failure was described allowing scientists to recognize early signs of the condition in females such as menstrual abnormalities facilitating early diagnosis and efficient management of symptoms.

Concise Articles

Adrenoleukodystrophy (ALD)

Poxel, winner of the 2023 edition of the I-nov contest

https://www.poxelpharma.com/en_us/news-media/press-releases/detail/252/poxel-winner-of-the-2023-edition-of-the-i-nov-contest

Canavan Disease

Burjeel Holdings to Launch Rare Disease Research & Development Project 'NADER' in Partnership with US-based BridgeBio Pharma

https://bridgebio.com/news/burjeel-holdings-to-launch-rare-disease-research-development-project-nader-in-partnership-with-us-based-bridgebio-pharma/

GM1 and GM2 Gangliosidosis

New Hope Research Foundation and Forge Biologics Announce cGMP Manufacturing Partnership to Accelerate Gene Therapy for Patients with Tay-Sachs Disease

https://www.forgebiologics.com/new-hope-research-foundation-and-forge-biologics-announce-cgmp-manufacturing-partnership-to-accelerate-gene-therapy-for-patients-with-tay-sachs-disease/

TAYSHA GENE THERAPIES PROVIDES CLINICAL UPDATES FOR INVESTIGATIONAL PROGRAMS TSHA-120 IN GIANT AXONAL NEUROPATHY (GAN) AND TSHA-102 IN RETT SYNDROME AT R&D DAY

https://ir.tayshagtx.com/news-releases/news-release-details/taysha-gene-therapies-provides-clinical-updates-investigational

Leukodystrophy

Medtech: BrainTale gathers €4.5 million to accelerate the development of its solution for diagnosis, monitoring and prediction of neurological disorders

https://www.braintale.eu/medtech-braintale-gathers-e4-5-million-to-accelerate-the-development-of-its-solution-for-diagnosis-monitoring-and-prediction-of-neurological-disorders/

Metachromatic Leukodystrophy (MLD)

Orchard Therapeutics Announces Second Closing of Strategic Financing, Resulting in $34 Million of Additional Capital

https://ir.orchard-tx.com/news-releases/news-release-details/orchard-therapeutics-announces-second-closing-strategic