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)

Neurocognitive and mental health impact of adrenoleukodystrophy across the lifespan: Insights for the era of newborn screening
https://onlinelibrary.wiley.com/doi/10.1002/jimd.12581

This article reviews the neurological and mental implications of adrenoleukodystrophy (ALD) and its effects on patients and their families. ALD is a genetic neurodegenerative disorder characterized by a progressive loss of neurons in the nervous system, affecting the patient's ability to perform simple daily tasks. ALD mostly affects males with 35-40% of them developing cerebral ALD (cALD) during childhood. It is the most aggressive type of ALD causing a rapid and radical loss of myelin sheath in neurons and progressive brain inflammation leading to serious neurological impairments. Nonetheless, most male patients develop adrenomyeloneuropathy (AMN) a condition related to spinal cord defects caused by ALD with symptoms including muscle weakness and neuronal pain. In order to diagnose the condition, a screening panel in the United States was created offering the patients an opportunity for early treatment ameliorating the symptoms and increasing the survival rate. Early treatment will allow the patients to increase their independence and complete daily tasks without the need for constant intervention. This will also enhance the patient's confidence and mental well-being. Nevertheless, patient independence will also ease the interference of family and caregivers, improving their welfare. Overall, ALD has detrimental effects on patients' physical and mental health as they are often unable to look after themselves and complete daily tasks. Early screening diagnosis makes it feasible to immediately treat the disease and ameliorate the daily life for the patients and their families.

Low donor chimerism may be sufficient to prevent demyelination in adrenoleukodystrophy
https://onlinelibrary.wiley.com/doi/10.1002/jmd2.12259

In this case, the efficacy of unrelated cord blood transplantation (UCBT) to treat adrenoleukodystrophy (ALD) is explained in order to prevent demyelination in patients. ALD is a genetic, inherited condition affecting the cells of the nervous system and leading to neurological and congenital impairments. It is caused due to mutations on the ABCD1 gene responsible for producing a transfer protein able to translocate very-long-chain fatty acids (VLCFA) from the cell membrane to the organelles that metabolize them. This mutation, therefore, allows the accumulation of VLCFA into the cells of the nervous system resulting in impaired metabolic pathways and cell death. The main treatment of the disease includes hematopoietic stem cell transplantation (HSCT) where stem cells from a healthy donor are inserted into the patient. In this case report, the usage of unrelated cord blood transplantation (UCBT) was used as a donor source for HSCT to treat ALD. This method has a

low risk of graft failure, increasing the treatment's efficiency and hence the symptoms' amelioration. After the UCBT the patient was found to have a low ratio of donor-to-recipient cells whilst MRI showed no brain deterioration. Overall, in follow-up appointments, a halt in the progression of the condition was noted suggesting HSCT treatment with UCBT as a possible treatment for ALD.

Poxel Receives Orphan Drug Designation from the European Commission for PXL770 and PXL065 for Treatment of Adrenoleukodystrophy
https://www.poxelpharma.com/en_us/news-media/press-releases/detail/234/poxel-receives-orphan-drug-designation-from-the-european

Newborn Screening for X-Linked Adrenoleukodystrophy: The Initial Illinois Experience
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8788425/

The rare, rapidly progressing, neurodegenerative disorder X-linked adrenoleukodystrophy (X-ALD) is caused by a mutation in the *ABCD1* gene. As treatment is possible prior to the onset of neurological symptoms, early diagnosis is very important and can be lifesaving. Therefore, X-ALD has been added to newborn screening in various states, this review describes the initial experience of implementing this in Illinois. Over three years there were 276,00 newborns tested, this was done by measuring levels of the X-ALD biomarker C26:0 lysophosphatidylcholine in dried blood spots which is elevated in effected newborns. Samples below the negative cutoff were reported as negative, while samples between the negative and positive cutoff were considered borderline, therefore a second dried blood spot was tested to confirm results. Patients with a positive result were recommended to have follow-up testing where plasma very long fatty-chain acids (VLFCAs) were measured. If elevated the next step was *ABCD1* gene sequencing to determine if a genetic variant was detected. The false-positive rate during this screening series was low. Of the 276,000 infants screened, 91 had either an initial positive or borderline result, 33 were referred for diagnostic testing and 17 were diagnosed with X-ALD and 3 with a different peroxisomal disorder. This means that 52% of infants referred for diagnostic testing had a positive diagnosis, depicting the importance of newborn screening for X-linked adrenoleukodystrophy.

Alexander Disease

Case report: Alexander's disease with "head drop" as the main symptom and literature review
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9807021/

In this case report, a patient affected by Alexander's disease (AxD) exhibited a 'head drop' symptom as the main manifestation of the condition. AxD is an inherited, neurogenerative condition caused by mutations in the GFAP gene coding for the glial fibrillary acidic protein (GFAP). This mutation leads to overaccumulation of GFAP in the cells of the nervous system resulting in a variety of symptoms including muscle weakness, epilepsy, spasticity and psychomotor retardation. There are three subtypes of AxD depending on the onset age of symptoms. Infantile AxD refers to patients until 2 years of age, juvenile AxD refers to patients until 13 years of age and adult AxD refers to patients above 13 years of age. In this case, a 4-year-old girl was diagnosed with juvenile AxD with the main symptom being a head-drop movement. An MRI conducted, showed abnormal signal detection suspecting the presence of AxD. Gene detection analysis revealed a mutation in the GFAP gene leading to the

diagnosis of the condition. Overall, a head-drop movement is not a usual symptom of juvenile AxD but diagnostic techniques involving gene detection allowed the diagnosis of AxD in a 4-year-old patient.

Cerebral Autosomal Dominant Arteriopathy with Subcortical infarcts and Leukoencephalopathy (CADASIL)

Active immunotherapy reduces NOTCH3 deposition in brain capillaries in a CADASIL mouse model
https://www.embopress.org/doi/full/10.15252/emmm.202216556

This article reviews the efficacy of active immunotherapy to reduce NOTCH3 accumulation in the brain allowing the treatment of cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL). CADASIL is an inherited arteriopathy affecting the cerebral small vessels and resulting in neuronal loss, thickening of the arterial walls, and creation of white matter lesions. The condition is caused due to mutations in the NOTCH3 gene, which plays a vital role in the smooth muscle cells, allowing the NOTCH3 product to accumulate in the cells. The main symptoms of the disease range from migraines to ischemic events where blood flow and oxygen are restricted in a part of the body and severe cognitive impairments. Nonetheless, currently there is no treatment available to halt the progression of CADASIL. However, a new treatment involving active immunotherapy revealed a reduced NOTCH3 accumulation in the brain. Specifically, active immunotherapy targets the NOTCH3 gene pathology leading to a reduction of the gene product in the capillaries suggesting the treatment is efficient. An active immunotherapy treatment against the accumulation of NOTCH3 product was found to be successful in a mouse model suggesting this is a possible treatment for the condition. Further research must be made to properly understand the underlying mechanism of the therapy's action to evaluate its efficiency and safety.

Metachromatic Leukodystrophy

An international study of caregiver-reported burden and quality of life in metachromatic leukodystrophy
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9438185/

Identification of neurodegeneration indicators and disease progression in metachromatic leukodystrophy using quantitative NMR-based urinary metabolomics
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8898726/

Adrenomyeloneuropathy (AMN)

The Lancet Neurology publishes results from Minoryx Therapeutics Phase 2/3 ADVANCE clinical trial of leriglitazone in X-linked Adrenoleukodystrophy
https://www.minoryx.com/media/the-lancet-neurology-publishes-results-from-minoryx-therapeutics-phase2-3-advance-clinical-trial-of-leriglitazone-in-x-linked-adrenoleukodystrophy/

Minoryx Therapeutics works on the development of treatments for central nervous system disorders. Results are now published from the first and largest international study to include adult male X-linked adrenoleukodystrophy (X-ALD) patients for their lead candidate leriglitazone, assessing its efficacy and safety in male patients with adrenomyeloneuropathy (AMN). In its Phase 2/3

ADVANCE clinical trial, there were 116 randomized patients with 77 receiving leriglitazone and the other 39 a placebo. It was generally well tolerated, with clinically relevant differences in body sway measurements and positive trends for the Expanded Disability Status Scale (EDSS), the Severity Scoring system for Progressive Myelopathy (SSPROM), and quality of life. The EDSS measures neurological disability and the SSPROM measures the severity of myelopathy. An important result was it showed reduction in the progression of cerebral lesions and only those in the placebo group developed clinically progressive cerebral ALD (cALD). At week 96 in placebo patients with progression of cerebral lesions, the plasma biomarker neurofilament light chain had significantly increased levels, thus supporting the positive effect leriglitazone has on reducing axonal damage. Also at week 96, a significant increase in the Loes severity score was seen in the placebo group, this rates the severity of abnormalities found in MRI scans of the brain in order to assess disease progression and treatment effectiveness. Since the drug was found to have potential for benefit, it will now continue as an open label extension study where all participants, including those previously in the placebo group, will be given leriglitazone. This will allow further monitoring of the progression of myelopathy and cerebral lesion and the impact of treatment with leriglitazone.

Cockayne syndrome (CS)

UMass Chan researchers achieve gene therapy milestone for potential Cockayne syndrome treatment
https://www.umassmed.edu/news/news-archives/2023/01/umass-chan-researchers-achieve-gene-therapy-milestone-for-potential-cockayne-syndrome-treatment/

Giant Axonal Neuropathy (GAN)

TAYSHA GENE THERAPIES PROVIDES UPDATE ON TSHA-120 PROGRAM IN GIANT AXONAL NEUROPATHY AND A 2023 CORPORATE OUTLOOK
https://ir.tayshagtx.com/news-releases/news-release-details/taysha-gene-therapies-provides-update-tsha-120-program-giant

Taysha Gene Therapies is focused on developing adeno-associated virus (AAV) based gene therapies to treat rare central nervous symptom disorders such as giant axonal neuropathy (GAN). They currently have a program, TSHA-120 specifically for GAN. Following a Type B end-of-Phase 2 meeting with the Food and Drug Administration (FDA), two updates were provided. Their approach for the manufacturing of a pivotal/to-be marketed product was deemed appropriate, pending review of their Chemistry, Manufacturing, and Controls (CMC) data package for TSHA-120. The FDA also acknowledged that MFM32 is an acceptable endpoint and provided some recommendations to support their biologics license (BLA) application submission which Taysha is clarifying with the FDA.

Krabbe Disease

Forge Biologics Receives Priority Medicines (PRIME) Designation from the European Medicines Agency (EMA) for Novel Gene Therapy FBX-101 for the Treatment of Patients with Krabbe Disease
https://www.forgebiologics.com/forge-biologics-receives-priority-medicines-prime-designation-from-the-european-medicines-agency-ema-for-novel-gene-therapy-fbx-101-for-the-treatment-of-patients-with-krabbe-disease/

Following review of the positive safety and efficacy data from Forge Biologics Phase 1/2 RESKUE clinical trial, the European Medicines Agency (EMA) have granted Forge Biologics priority medicines designation (PRIME) to FBX-101. This is their adeno-associated virus (AAV) drug candidate and novel gene therapy for the treatment of patients with Infantile Krabbe disease. This rare neurodegenerative disease is caused by autosomal recessive mutations in the galactocerebrosidase (GALC) gene. During the trial, it was demonstrated as safe and well tolerated in patients who received FBX-101 intravenously after hematopoietic stem cell transplant (HSCT). Thus, delivering a functional copy of the GALC gene to cells in the nervous system. Compared to untreated patients or those only treated with HSCT, restoration of GALC enzyme activity, reduced psychosine, promising signs of normal myelination, and improved motor development was observed in patients who received FBX-101. PRIME will provide Forge Biologics with earlier and proactive support to aid in the development of their gene therapy which patients will benefit from earlier access to.