Adrenoleukodystrophy

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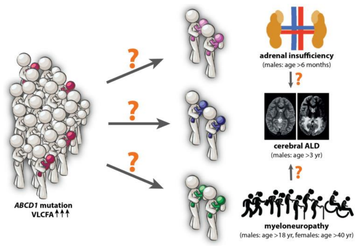
Background

Adrenoleukodystrophy (ALD) is an X-linked genetic condition. This causes an inability to break down very long chain fatty acids (VLCFAs). VLCFA buildup damages myelin sheath on nerves. This can lead to severe neurological function loss and can lead to adrenomyeloneuropathy (AMN), a slowly progressive spinal cord disease. AMN largely impacts males from 30-40 years old and post-menopausal women.



35%-45% of males with ALD suffer from Cerebral ALD (CALD). In CALD, individuals between 3-10 years old suffer from rapid inflammatory cerebral demyelination. Notable symptoms are loss of senses and coordination, general illness, and a loss of neurological function. Untreated, CALD often leads to death.

Statistics

Impacts 1 in 14,700 individuals

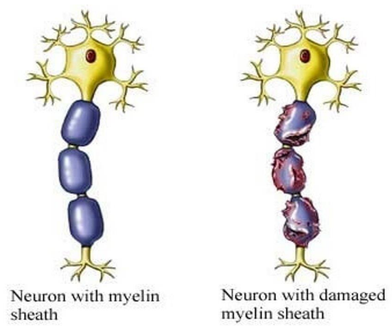
With early treatment, about 94% survival from CALD

80% of males suffer adrenal insufficiency leading to Addison's disease

Of males with AMN, about 20% develop cerebral disease leading to disability and death

Molecular Pathway of ALD

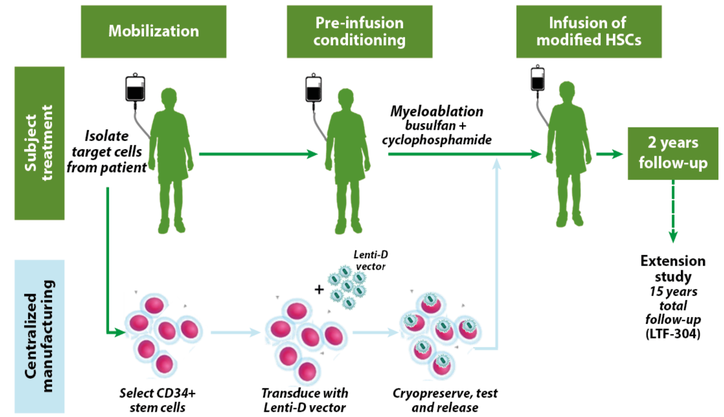
- The pathognomonic accumulation of straight chain, saturated VLCFAs (i.e., made up of more than 22 carbon atoms) is the hallmark of this disease.
- The accumulation of VLCFAs is the result of an abnormality in their degradation.
- Reduced activity of the enzyme VLCS that activates VLCFAs to their CoA derivatives, the substrate for the β-oxidation cycle in peroxisomes, results in pathognomonic accumulation of VLCFAs in tissues such as the adrenals, testes, and brain in X-ALD patients.
- Consequently, they are the cause of the metabolic disease in X-ALD.



- ALD can be diagnosed at birth, but the clinical course cannot be predicted. Patients are pre-symptomatic at birth.
- ALD research should investigate if an increase in MCP-1 or chitotriosidase occurs before, or as a consequence of, the neuroinflammation and damage to the BBB during the onset of cerebral ALD, and if they could be an early predictive biomarker for cerebral ALD.
- In addition, as shown in Alzheimer's disease clinical trials targeting neuroinflammation , chitotriosidase and perhaps MCP-1 could serve as pharmacodynamic markers of neuroinflammation, specifically microglial activation, which would be relevant for use in cerebral ALD clinical trials.
- NfL may be suitable as a general dynamic marker of neuro-axonal injury for ALD, with longitudinal measurements being used to monitor disease activity and response to treatment in ALD clinical trials.
- For example, NfL levels in the blood will be affected by peripheral neuropathy, in addition to factors such as an individual's body mass index or blood volume.

A Therapeutic Targeting the Alteration

Hematopoietic Stem Cell Transplantation (HSCT): reported stabilization (and possibly reversal) of neurological changes that persists for five to ten years (Moser, 2012)



Other Therapeutic Explorations

Hormone replacement therapy

Mandatory for all X-ALD patients who have primary adrenocortical insufficiency (Moser, 2012)

Dietary therapy with Lorenzo oil

Oral administration of this oil, with reduction of fat, significantly lowers the levels of VLCFA in the plasma of patients within four weeks. (Moser, 2012)

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