

The Pathogenesis of Adrenoleukodystrophy

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ABSTRACT

Adrenoleukodystrophy (ALD) is a rare, inherited disorder that affects the brain, spinal cord, and adrenal glands. It is caused by mutations in the ABCD1 gene, which provides instructions for making a protein called ABCD1, which is involved in the metabolism of very long-chain fatty acids (VLCFAs). In ALD, the body cannot properly break down and clear VLCFAs, which can lead to the accumulation of these fatty acids in the brain and other tissues. This accumulation can cause inflammation and damage to cells and tissues, leading to various symptoms. Symptoms of ALD may vary depending on the type of ALD and the severity of the condition. Common symptoms include neurological problems, such as difficulty walking, speaking, behavioral changes, and problems with the adrenal gland, such as adrenal insufficiency which is a condition in which the adrenal glands do not produce enough hormones. ALD is a progressive disorder, meaning symptoms may worsen over time if left untreated. Treatment for ALD typically involves medications and supportive care to manage symptoms and prevent complications. Sometimes, a bone marrow transplant may be recommended to replace damaged cells and tissues. Genetic testing is available for ALD and can be used to diagnose the disorder and identify people at risk of developing it. Early diagnosis and treatment can help improve the chances of a full recovery and a good quality of life for people with ALD.

Introduction

X-linked Adrenoleukodystrophy (ALD) is a serious neurodegenerative disorder that results in the loss of myelin in the central and peripheral nervous systems and affects the adrenal cortex. There are two main subtypes of this disorder: a rapidly progressing form that affects children and a slower form that affects adults. The adult form, called Adrenomyeloneuropathy, presents as a slowly progressing weakness in the legs. However, these different subtypes of the disorder are often misdiagnosed.

This condition affects 1 out of every 17000 individuals [1]. The two primary ALD phenotypes are The kind of cerebral demyelination, which primarily affects children between the ages of 5 and 12, and 35% of adults. The spinal cord primarily affects males between the ages of 20 and 50, as well as 50% of heterozygous females. Addison's illness may be the first indication of ALD in boys and adult males. These patients are permanently at risk of developing cerebral ALD or AMN.

Molecular and Genetic Basis of ALD

The aberrant buildup of saturated VLCFAs, especially hexacosanoic (C26:0) and tetracosanoic (C24:0) acids, is the main metabolic anomaly in X-ALD. Tetracosanoic acid is often referred to as lignoceric acid. The quantity of saturated VLCFAs with long carbon chains of 28, 30, and longer, and the levels of monounsaturated VLCFAs C24:1 and C26:1, are also increased. [2]

A mutation in the ABCD1 gene can alter both the genotype and phenotype and lead to the VLCFA protein's production. The ALD protein transports VLCFA or VLCFA-CoA into peroxisomes, broken down by

a process called peroxisomal beta-oxidation. The brain, after death, is expected to have higher levels of VLCFAs, but the specific types of lipid fractions that make up the excess VLCFA in X-ALD can vary based on the stage of the disease and the location of the tissue. [8] This suggests that the excess VLCFA is a consequence of demyelination rather than the cause of it.

ALD is typically diagnosed by measuring the levels of VLCFA in the blood. It typically only affects males. A male with a mutated version of the gene on his single X chromosome is hemizygous and cannot pass the disorder on to his male children, but all of his daughters will be carriers of the disorder. Female carriers who do not have the disorder can pass it on to their affected sons. This means that the disorder can be transmitted from affected males to their male grandchildren through carrier daughters, a process is known as "diagonal" or "Knight's move" transmission.

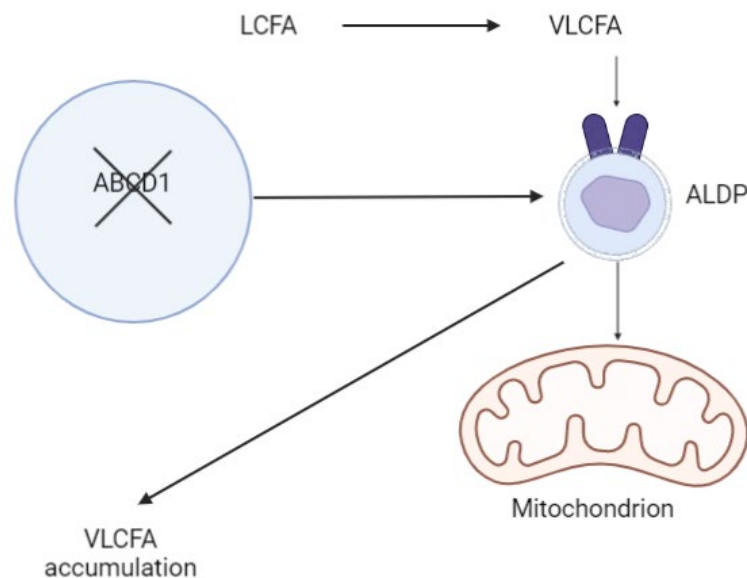


Figure 1. The loss of function of the ABCD1 gene leads to the accumulation of the VLCFA in the brain. ALDP suffers from upstream ABCD1 loss of function since it causes the reduction of the peroxisomal VLCFA β -oxidation. Therefore, there will be excess fat in the brain.

Childhood Cerebral ALD

Between the ages of three and ten, neurological symptoms appear in 35% of afflicted males. Before the age of about two and a half to three, it rarely happens. The affected males will grow normally before exhibiting a loss of previously learned skills. Affected boys may display behavioral issues such as attention deficit and hyperactivity disorder (ADHD) and learning challenges before losing skills. Affected people frequently experience cognitive deficiencies, which implies that their brain functions may be impaired and that they may struggle to learn new things. As a result, impacted kids might exhibit a drop in academic performance. They might "zone out" during class or other times, have trouble hearing or understanding spoken words, trouble reading or understanding written words, trouble with spatial references, and show a decline in handwriting abilities.[3]

As the condition progresses, people with ALD may experience additional symptoms such as decreased vision, hearing loss, difficulty walking, weakness and stiffness in the limbs, seizures, or convulsions. Ultimately, affected children lose most of their neurological function and become severely disabled with blindness, deafness, and the inability to move voluntarily. The disorder will eventually progress to the point where the

person is in a vegetative state and will die, usually within two to three years of the onset of neurological symptoms. [7]

Addison's Disease

Affected males may also have adrenal insufficiency. When the adrenal glands fail to produce these hormones, the term primary adrenal insufficiency is used. Symptoms can include fatigue, unintended weight loss, nausea, vomiting, gastrointestinal issues, weakness, morning headaches, low blood pressure (hypotension), and low blood sugar levels (hypoglycemia). These symptoms are reminiscent of Addison's disease. Many affected males may develop tanning of skin including areas not exposed to sunlight (hyperpigmented skin).[10]

In people with adrenoleukodystrophy (ALD), the body cannot properly break down and clear very long chain fatty acids (VLCFAs), which can lead to the accumulation of these fatty acids in the brain and other tissues. This accumulation can cause inflammation and damage to cells and tissues, including the adrenal glands, leading to adrenal failure and other problems.

The purpose of the literature review on ALD is to gain a more holistic insight how this rare disease is triggered. And even with the knowledge of the cause, many do not know that there are other factors that can possibly inhibit the development of this disease.

Methods

Step 1: Most of the resources used in the paper were from Pubmed. The keywords used: were ABCD1 gene, Addison's disease, learning disabilities, myelinization, and cerebral.

Step 2: the best articles were found through source identification. For example, the title would be the best indication of the sources genuinely. If it is a one-word title, it most likely was a review article. The research is more than a review, it's a gathering of the causes and treatments in a more in-depth way.

Step 3: 3-5 sources were found for the general overview of the topic, and I could reference off of them.

Step 4: After the paper is completed, charts and visual representations were used from Biorender.

Step 5: Finally, evidence on the treatments, was taken from Clinical Trials. Results were usually chosen from the completed trials and data would be plotted as a visual representation.

Results: Pathogenesis and Molecular Mechanisms of ALD [Current Research: Molecular and Clinical Approaches]

ALD from a Molecular Perspective

The ABCD1 gene encodes for the production of adrenoleukodystrophy protein (ALDP), ALDP is located in the membrane of cell structures called peroxisomes. Peroxisomes are small sacs within cells that price many types of molecules. When there is a mutation in the gene there will be a deficiency of the ALDP, the transport, and therefore disrupts the breakdown of very long fatty acid chains, then these fatty molecules build up in the tissues of the body. The abnormal accumulation of these fatty acids in the brain sets off an inflammatory response by the immune system that damages the myelin, leading to the symptoms associated with x-linked adrenoleukodystrophy.[6] When there is inflammation, the body's immune system sends white blood cells and other

substances to the affected area to fight off the perceived threat. This can cause swelling and pressure in the brain, leading to a range of symptoms depending on the severity and location of the inflammation.

The body is unable to properly break down and clear VLCFAs, which can lead to the accumulation of these fatty acids in the brain and other tissues. These glands produce hormones that help regulate various functions in the body, including stress response, blood pressure, and metabolism. In ALD, the adrenal glands may become damaged or malfunction, leading to problems with hormone production and other issues. And the root cause of the VLCFA malfunction is our body's inability to code for the ABCD1 gene.

ALD from a Clinical Perspective

To track the causes of cerebral adrenoleukodystrophy, scientists have decided to conduct an experiment that measures the growth of early cerebral lesions from longitudinal MRIs. This will compare the patients with progressive ALD and people who do not have it. 174 MRIs obtained from 36 presymptomatic male patients with cerebral adrenoleukodystrophy. The lesions were then segmented, and the lesion velocity acceleration was calculated and plotted. The result was that early-stage cerebral disease progression was inversely correlated with age, early lesions can grow while appearing radiographically stable. They go through sustained acceleration in progressive ALD. A total of 23 patients were used for the experiment.

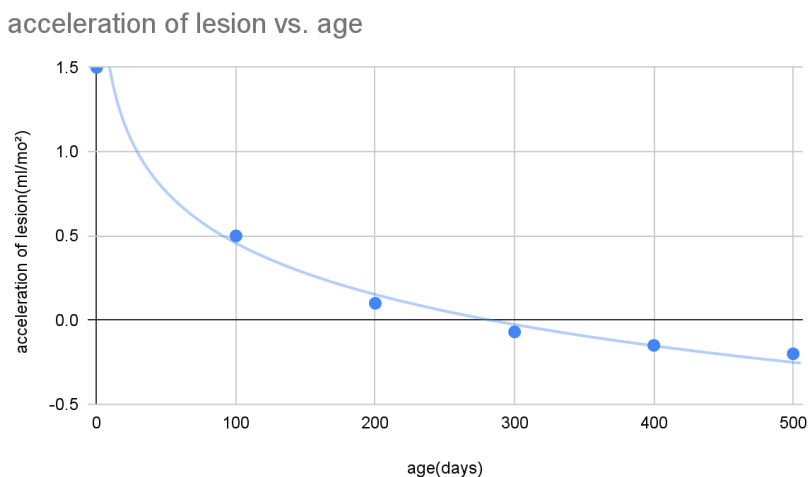


Figure 2. Acceleration of Lesions in Patients with ALD with age. Patients with ALD have a latency period before lesion development.

Childhood cerebral adrenoleukodystrophy (CCALD) is a life-threatening condition that usually requires a hematopoietic stem cell transplant to survive. Boys with CCALD should be closely monitored with regular brain MRIs during the most high-risk period.[7] It can take a very long time to diagnose CCALD, as children with the condition may not show symptoms for months or even years. Those who do show symptoms are likely to have poor outcomes from a stem cell transplant.

Discussion

Although the ABCD1 gene is responsible for the accumulation of recent studies have shown that there is a separate gene from the same area. In addition to ALDP, there are three other similar ABC half-transporters called ALDRP, PMP70, and PMP69 that are located on the membrane of peroxysomes. To work properly, ALDP must join with one of these half-transporters to form a full-transporter. Increasing the amount of ALDRP,

which is produced by the ABCD2 gene, has been shown to improve the production of very long-chain fatty acids (VLCFAs) in cells with X-linked adrenoleukodystrophy (X-ALD) and to reduce protein oxidative damage in a pilot trial of X-ALD patients treated with the drug valproic acid (VPA). Other substances that can increase the production of ALDRP include 4-phenylbutyrate, other histone deacetylase inhibitors, and certain ligands that bind to nuclear receptors such as PPAR alpha, thyroid hormones, and thyromimetics, retinoids, and LXR antagonists. Recently, it was discovered that the AMPK α 1 enzyme is reduced in X-ALD, which has led to the investigation of whether the drug metformin, which increases AMPK α 1, may be useful in the treatment of X-ALD

Genetic testing can diagnose ALD in people with symptoms and a family history of the disorder. It can also be used to identify people at risk of developing ALD, even if they do not have symptoms. Several types of genetic tests can be used to diagnose ALD, such as molecular genetic testing, which takes the specific mutation in the ABCD1 gene. Also, the chromosomal microarray analysis is helpful too, a test that looks for the change in the size or the number of chromosomes. Last but not least, the multi-Panel testing: This test looks for mutations in several genes simultaneously, including the ABCD1 gene. Genetic testing can be performed using a blood sample or a sample of cells from the inside of the cheek. The sample is then analyzed in a laboratory to look for mutations or other changes in the DNA. By concluding the variety of causes of Adrenoleukodystrophy, there would be more holistic and accurate treatments for it.

Limitations

Several limitations include limited access to research materials. Not all of the research materials are online or maybe it could be because of copyright. There is also limited time, where research papers all have tight deadlines, limiting the amount of time to make extensive research, and cause a comprehensive review of the literature. There is also a limited budget where funding constraints limit the scope of research, as many may not be able to afford to purchase the necessary materials or pay for access to certain databases. The limited expertise could also pose a limitation many individuals are not experts in this certain field.

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