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## Adrenoleukodystrophy an Overview

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### Abstract



Adrenoleukodystrophy (ALD) is a rare X-linked peroxisomal oxidation disease caused by mutations in ABCD1. It presents with various clinical manifestations, including cerebral ALD, myelopathy, and primary adrenal insufficiency. About 80% of ALD patients suffer from adrenal insufficiency, and cerebral ALD affects one-third of boys under twelve, progressing to total impairment and death without treatment. Hematopoietic stem cell transplantation (HSCT) is the only disease-modifying treatment for early-stage cerebral ALD, but it does not halt adrenal insufficiency progression and carries significant morbidity and mortality risks. A recent gene therapy clinical trial showed short-term MRI and neurological outcomes equivalent to past HSCT treatments without the adverse side effects. Additionally, over a dozen states have initiated newborn screening (NBS) for ALD, with the number expected to triple by 2020. Genetic testing of NBS-positive newborns has identified novel variations of unknown significance, raising questions about monitoring and treating preclinical or moderate adrenal insufficiency or cerebral involvement. This presents further opportunities for genetic characterization. The availability of matching donors, transplant centers, and specialists will impact prompt treatment for those diagnosed with ALD at birth. As NBS and gene therapy trials improve ALD's clinical management and prognosis, endocrine management of presymptomatic and subclinical adrenal insufficiency will become increasingly important.

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### INTRODUCTION

Pathogenic mutations in the X chromosome gene encoding the protein ATP-binding cassette subfamily D member 1 (ABCD1) cause Adrenoleukodystrophy, an X-linked progressive neurological illness. It is typified by insufficient  $\beta$ -oxidation, which causes peroxisomal saturated very long chain fatty acids (VLCFA) to accumulate in the brain white matter, adrenal glands, testes, and spinal cord [1]. Cerebral Adrenoleukodystrophy (ALD) was most likely the majority of cases of what was incorrectly called "Addison-Schilder disease" in the early 20th century. Still, other diseases were frequently

mistakenly identified at the time because no biomarker or DNA analysis was available.

On the X chromosome, the ABCD1 gene is where the mutations occur [2]. ALDP, a peroxisomal transmembrane protein that carries VLCFA acyl-CoA esters from the cytosol into the peroxisome, is absent or dysfunctional when this gene is mutated. Elevations of VLCFA in plasma or serum are crucial in diagnosing ALD because they accumulate in the tissues and the blood [3]. The gene has ten exons and codes for a 745 amino acid protein. A database is kept up to date with a list of the known disease-causing ABCD1 variations and variants with uncertain significance. More than 900 pathogenic variants have been reported [4]. Clinically, the results for boys and men with There are significant differences in ALD, ranging from isolated adrenal insufficiency to quickly worsening, fatal neurological dysfunction and chronic disability in adult individuals. VLCFA testing may have a 20% false-negative rate in females, which is insufficient. Recent research has demonstrated the superior diagnostic efficacy of C26:0-lysophosphatidylcholine (C26-lysoPC), with a sensitivity of >99% in identifying women with ALD, including those with normal plasma VLCFA levels. At a birth incidence of 1 in 17,000 neonates (male and female), X-ALD is the most common peroxisomal disease [5]. It happens everywhere in the world. The true prevalence may be higher now that newborn screening is technically feasible and may be introduced in various regions worldwide. With the recent implementation of newborn screening (NBS) for ALD, illness can be identified before it manifests clinically, and further genetic characterization and phenotyping are now possible. A potential new therapy for childhood cerebral ALD is emerging that combines gene therapy and autologous HSCT. (CCALD) [6]. The clinical management and outcomes of ALD are beginning to change due to these advancements in ALD screening and therapy. However, there are still many unanswered questions regarding the best timing for treatment, clinical care for women with ALD, and clinical monitoring for adrenal insufficiency and brain involvement before clinical manifestations. This overview reviews the significant developments in gene therapy and NBS and how they could change how endocrinologists treat ALD patients.

### **Pathogenesis:**

There is currently no complete model available to research the pathophysiological pathways of X-ALD. Many different tissues express ABCD1, and practically all tissues have significantly higher VLCFA levels. Clinically, endocrine tissue, including the adrenal glands and testes, the brain and spinal cord, and peripheral nerves are all impacted. It is uncertain why some cell types are specifically vulnerable to metabolic malfunction in X-ALD [7]. It is reasonable to believe that VLCFA deposits, a biochemical characteristic of X-ALD, are crucial to tissue destruction, but its specific pathophysiological mechanisms remain unknown. Observation of the clinical course of X-ALD and investigations of the etiology of X-ALD indicate the involvement of two unique but interconnected processes. ABC transporters work as dimers made up of two connected halves. ALDP is referred to as a half-transporter since it only represents one of these halves [8]. When two half-transporters are bound, a functioning transporter is produced, and the substrate passes through a channel formed by the two membrane domains. A hydrophobic membrane domain with six membrane-spanning segments is present in each ABC half-transporter. It has been established that ALDP can create a homodimer. However, three more ABC transporters, PMP70, PMP69 (P70R), and the ALD-related protein (ALDR), are present in the peroxisomal membrane. With sure of them, it can also form heterodimers. Because it shares 66% of ALDP's identity and can perform ALDP's role in restoring the ability of ALD fibroblasts to metabolize VLCFA, ALDR, which has been mapped to 12q11, is of great relevance. The disease's phenotypic expression may be affected by ALDP and its homologs. ALDP deficiency impairs VLCFA beta-oxidation (around 30% of normal) and causes VLCFA-CoA esters to accumulate in cells [9]. Various lipid fractions absorb the cytosolic VLCFacyl-CoA esters, which act as a substrate for further elongation to produce even longer fatty acids. A single elongase called ELOVL1 (elongation of very long-chain fatty acids) is responsible for the synthesis of both monounsaturated (C26:1) and saturated (C26:0) VLCFA. More remarkable VLCFA synthesis is caused by higher substrate availability in X-ALD fibroblasts, even though ELOVL1 expression is not elevated in these cells [10]. The VLCFA homeostasis is impacted in

X-ALD. This could potentially exacerbate the instability of the myelin sheath and interfere with the activity of microglia and astrocytes, two critical components of myelin integrity. Not all males with X-ALD develop cerebral ALD, supporting the theory that this process is influenced by various genetic, epigenetic, and/or environmental causes. Since there isn't a suitable X-ALD animal model that causes cerebral demyelination together with neuroinflammation, it's unclear what pathogenic mechanisms lead to cerebral demyelination and, eventually, severe neuroinflammation.

### **Clinical features:**

Historically, attention deficit and hyperactivity disorder (ADHD), school failure, language comprehension problems, deviant behavior, and handwriting deterioration were the first signs that led to the diagnosis of ALD in males. This was determined through neuroimaging. Addison-only, childhood, teenage, and adult cerebral ALD, adrenomyeloneuropathy (AMN) with or without cerebral demyelination, and symptomatic or asymptomatic carriers are among the numerous phenotypes that make up X-ALD that are typically reported [11]. X-ALD was an unknown illness for most of the 20th century, despite some theories that it might be a metabolic condition affecting the adrenal glands and central nervous system. According to Schaumburg and Powers, the illness may be a lipid storage disorder. They proposed the term "adrenoleukodystrophy" based on observing lipid inclusions in the brain, testis, adrenal glands, and Schwann cells. This theory was supported by the discovery that seven patients' serum, adrenal glands, and brains all had high cholesterol esters containing fatty acids longer than C22 after death. We called these fats "very long-chain fatty acids" (VLCFA). Addison's illness, which is linked to spastic paraplegia, was first described in 1910. In 1976, progressive myelopathy with adult-onset that was X-linked and frequently connected to Addison's illness was discovered. Because the adrenal cortex, spinal cord, and peripheral nerves were all affected, the term adrenomyeloneuropathy (AMN) was proposed after five additional instances were reported a year later [12]. Because plasma VLCFA analysis is a recently discovered biomarker. The phenotypic spectrum of X-ALD was soon extended when it was found that AMN is a form of the

disease. Patients with X-ALD are asymptomatic at birth, but over time, myelopathy will develop, albeit at a highly variable age. Nearly all males with X-ALD develop adrenocortical insufficiency during life, about 80% before adulthood. There are occasionally signs of testicular insufficiency, though these are typically not clinically apparent. Most men with X-ALD have thin scalp hair, and many have premature balding. A myelopathy eventually develops in almost all male patients with X-ALD; this usually happens in the third or fourth decade of life [13].

In most cases, urge incontinence is the first symptom, which is usually followed by a spastic gait. Adrenomyeloneuropathy (AMN), the term used to describe the combination of X-ALD peripheral neuropathy and myelopathy, affects all men with the disease eventually. However, the age at which it first manifests and the speed at which it progresses varies greatly. Cerebral ALD can also be brought on by infections or head trauma. In children with cerebral ALD, cognitive impairment often presents as behavioral issues and a decline in academic performance. Then, there are localized neurological abnormalities that manifest as hemiparesis, dysarthria, dysphagia, visual and auditory agnosia, and occasionally epileptic seizures. Rarely, cerebral ALD stabilizes on its own, known as "arrested" cerebral ALD. It can come back to life years later [14]. After the age of 60, about 80% of women with X-ALD show signs of peripheral neuropathy or myelopathy. Rarely does an adrenal cortex fail. (18) To sum up, all male patients with X-ALD have peripheral neuropathy and chronic myelopathy, whether or not they have adrenocortical insufficiency. In contrast, over 80% of female patients with X-ALD are older than 60. This is the primary X-ALD phenotype. Cerebral demyelination can be difficult in male individuals and very seldom in female patients if it advances rapidly [15].

### **Diagnosis**

Historically, the diagnosis of ALD in boys was made by neuroimaging after the onset of early signs of attention deficit and hyperactivity disorder, academic failure, language comprehension challenges, behavioral disorders, and deterioration in handwriting. In the early 1980s, measuring very long-chain fatty acids in plasma provided a valid diagnostic test. Cultured

amniocytes and chorion villus cells had higher VLCFA levels, which enables the prenatal diagnosis of hundreds of affected male fetuses [16]. However, using DNA analysis to confirm is encouraged. According to brain magnetic resonance imaging (MRI), women heterozygous for X-ALD had more significant plasma VLCFA levels, but it is possible to get false-negative test findings. In carriers, DNA-based diagnosis is dependable. The possibility of using neonatal screening for ALD was realized as elevations in VLCFA were shown to be present at delivery. Brain MRI results in patients with pure AMN and heterozygotes are frequently normal. Patients with AMN have nonspecific cord atrophy on spinal cord MRI; however, quantification is possible due to magnetization transfer. With a reported sensitivity of 100% in 49 females and 126 controls, the Academic Medical Centre in Amsterdam has shown that the C26:0-LPC assay accurately diagnoses males with ALD. More importantly, it provides an accurate diagnostic test for women with ALD, as well, having developed whole blood spot liquid chromatography-tandem mass spectroscopy (LC-MS/MS) measurement of C26:0-lysophosphatidylcholine, C26:0-LPC. X-ALD can be diagnosed by demonstrating the biochemical abnormality and using mutation analysis. We advise using the plasma VLCFA assay<sup>10</sup> to diagnose males, which shows unusually high levels of C26:0 and abnormally high ratios of C24:0 and C26:0 to C22:0. Prenatal diagnosis has commonly been performed utilizing the VLCFA assay in cultivated chorion villus cells or amniocytes [17].

### Treatment

Currently, different types of therapy are offered. When administered in the early stages of the disease, they considerably improve the prognosis for X-ALD, although there is no known cure for this condition.

### Adrenal Replacement Therapy

More than 70% of male X-ALD patients have adrenal insufficiency, necessitating the administration of replacement adrenal hormone therapy. At the age of 6 to 12 months, patients with a compromised adrenal reserve can be recognized and treated. ALD accounts for most cases of adrenal insufficiency in males under 15 [18]. Female carriers are typically not impacted. The

most sensitive markers of adrenal dysfunction are elevated plasma ACTH concentration and decreased rise in plasma cortisol concentration in response to administered ACTH. Avoiding an adrenal crisis, which in the past significantly raised morbidity and death, improves general vigor and well-being. Nevertheless, conclusive proof of steroid replacement therapy's detrimental effects on cerebral development is still lacking.

### Lorenzo's oil [19][20]

Within four weeks, plasma VLCFA levels in X-ALD patients stabilize when Lorenzo's oil, a 4:1 blend of Monounsaturated oleic acid (C18:1) and monounsaturated erucic acid (C22:1), both in the form of triglycerides (glyceryl- trioleate), is administered. Due to the significant function that VLCFAs play in the pathogenesis of ALD, oleic acid alone was used in the first attempts to normalize the VLCFA in ALD. Recent studies indicate that Lorenzo's oil therapy may considerably lower the likelihood of acquiring cerebral disease, even while it does not affect the progression of the disease once it has started. Closely supervised For asymptomatic boys with X-ALD who have a typical MRI result, especially those who are younger than eight years old, Lorenzo's oil therapy is advised and is currently available as part of a research program. This must be accompanied by monitoring of the brain MRI as well as the recommended adrenal hormone replacement medication. Hematopoietic stem cell transplantation (HSCT) should be an option for patients who exhibit early signs of cerebral involvement. Lorenzo's oil was given along with a low-fat diet to 89 asymptomatic boys with ALD in an open, non-placebo-controlled investigation.

On the other hand, the percentage of boys who would develop CALD was 37%, which suggests a protective effect when compared to historical data. Twenty-four percent had CALD at a mean follow-up of 6.9 years. Since Lorenzo's oil barely penetrates the blood-brain barrier, it remains to be determined if it is truly beneficial in the central nervous system. Although Lorenzo's oil has been demonstrated not to affect the progressive nature of the disease in patients with cerebral disease, a recent study revealed that it may considerably lessen the likelihood of cerebral disease in asymptomatic males with normal brain MRI

results. The FDA has not authorized Lorenzo's oil therapy since a double-masked, placebo-controlled trial was not completed. Lorenzo's oil has not been shown in open-label studies to stop or delay the disease progression in either AMN or CALD.

### **Intravenous Immunoglobulin**

IVIGs have many effects, including regulating harmful autoantibodies, inhibiting complement activation, and inhibiting cytokines. Previously, IVIG was reported to minimize neuropathic pain related to the inflammatory condition Sjögren's syndrome and to lessen pain and significantly enhance motor function in proximal diabetic neuropathy. Although IVIG therapy has not yet been described in AMN, it has been given to ALD patients in the past without clearly slowing the progression of their condition, and it is not now advised as a treatment. IVIG was quite effective at treating pain, but it's still unknown if it affected the course of the disease, avoided brain axonal damage, or stabilized the mI/Cr [21]. Intravenous immunoglobulin (IVIG) has been tested as a potential treatment strategy. IVIG was used to treat a Japanese child, age 15, who had cerebral ALD. He took 100 mg/kg/day for five days straight, then 100 mg/kg/day every two weeks. His symptoms started to get better two weeks after commencing therapy, and no neurological decline was noticed for 18 months after beginning therapy. VLCFA levels and brain C.T. scans, strangely, did not change. Comparing the outcomes of a 1-year trial of IVIG treatment in 6 patients who were also receiving a restricted diet and Lorenzo's oil therapy to a control group of 6 ALD patients who only received diet and Lorenzo's oil therapy, our organization's research was conducted on six patients. All patients had normal VLCFA levels after two months, but both groups continued to advance similarly regarding neurologic symptoms and MRI abnormalities [22].

### **Hematopoietic Stem Cell Transplantation:**

In the inflammatory cerebral types of X-ALD, hematopoietic stem cell transplantation has been demonstrated to have long-term benefits. A recent study on the HSCT experience in cerebral ALD from 1982 to 1999 was published. The neurological condition at the time of the transplant directly affects the outcome of HSCT. The best outcomes appear in patients with MRI

involvement and minimal neurologic impairment. Patients can frequently anticipate ongoing demyelination because the condition is progressive, even after HSCT, until stabilization takes place. As a first-line treatment for patients with no symptoms, HSCT is not advised because up to 50% of those with regular MRIs may not develop cerebral illness. For patients who lack an excellent HLA-matched related or unrelated donor, HSCT is not even a therapeutic option [23]. There is a tiny window of opportunity for intervention once symptoms appear due to the disease's progressive nature, and the typical search period of several months is required to find an unrelated bone marrow donor if no suitable HLA-matched family member is available. Using cord blood units for transplantation has several benefits, including the capacity to accept more mismatches and speedy unit availability. The increased infection hazards frequently outweigh these benefits, prolonged time to engraftment and decreased likelihood of receiving an appropriate cell dosage in patients weighing more than 20 kilograms [24].

### **GENE THERAPY**

In 2009, the findings of the first gene therapy experiment, including two patients with childhood-onset cerebral ALD and no matched donors, were released. A trial of autologous HSCT with ex vivo lentiviral gene correction of CD34-positive stem cells is being conducted to lessen the morbidity burden of allogeneic HSCT. Following being myeloablative treated, the patients were reinfused with the genetically repaired ex vivo cells using a lentiviral vector producing wild-type ABCD1. However, prior research has shown a strong correlation between the use of gene therapy in hematopoietic cell populations and an increased risk of hematologic malignancy [25]. Adult patients with cerebral demyelination who have ALD, approximately 40% of these patients will not survive HSCT, may also be treated with gene therapy. Given that the neurologic advantages of gene therapy in ALD were equivalent to those seen with HSCT and that these patients had cerebral demyelination and no cord blood or available HLA-matched donors, additional research into this treatment is warranted. Several genetic disorders share ALD's extensive phenotypic expression as one of their defining traits [26]. The need for additional predisposing genes or spontaneous variation are

the two possible causes. Good candidates include the genes that code for the ABC peroxisomal transporters that would join ALDP to form a full ABC transporter. These modifier genes may also influence the immune response typical of the advanced type of cerebral ALD. The normal ALD gene is already being targeted in CD34 cells, which are hematopoietic stem cells, and retrovirus-mediated transfer of ALD cDNA normalizes VLCFA oxidation and content in ALD fibroblasts [27]. This procedure may be the best gene therapy approach before transferring the ALD gene directly into the central nervous system. Ten to twenty percent of all glial cells are microglial cells. Genetically engineered microglial cells may generate metabolic cooperation or other cell-contact-dependent processes that allow corrected metabolites to be transmitted to astrocytes and oligodendrocytes. Gene therapy will soon be combined with brain transplantation of glial cells or growth factor injection to promote myelin repair. The requirements of oligodendrocyte progenitors and their progeny for growth and survival factors are now fully recognized [28].

## CONCLUSION

This overview of ALD outlines our knowledge of the pathogenic mechanisms related to ABCD1 and VLCFA and the justification they offer for the current experimental therapy approaches. The therapy options for the fascinating disorder X-ALD are minimal, and its causes are still not fully understood. Neurologists should consider this when determining differential diagnoses in both men and women. For patients with ALD, there is hope thanks to current research on Intravenous Immunoglobulin, promising findings from a gene therapy experiment that is still in progress, and the expansion of newborn screening programs.

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