Adrenoleukodystrophy

Adrenoleukodystrophy (ALD) is a genetic disorder that is mostly inherited in an X-linked recessive pattern. It is caused by a mutation of the ABCD1 gene that leads to peroxisomal dysfunction and accumulation of very-long-chain fatty acids (VLCFAs) in different tissues. The clinical presentation is heterogeneous, and the ALD phenotypes are used to describe cerebral, adrenal and spinal cord, and peripheral nerve involvement. Males can present from childhood through adulthood, while female carriers present with a milder course and a later onset. Laboratory findings reveal high plasma levels of VLCFAs. Neuroimaging may reveal demyelination in the cerebral white mattering the cerebral forms of ALD. Diagnosis is confirmed by genetic testing. Treatment depends on the clinical presentation. Patients with early stages of cerebral involvement are candidates for hematopoietic stem cell transplantation (HSCT). Other treatments, such as Lorenzo's oil, have not demonstrated enough evidence in clinical studies.

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Pathophysiology

X-linked Recessive
X-suit with Recessive-chocolate
Adrenoleukodystrophy (ALD) is mostly inherited in an X-linked recessive pattern. Males present with a more severe clinical presentation and may present in childhood. Female carriers usually develop symptoms in adulthood, but adrenal and cerebral involvement is rare in them.

Peroxisome Dysfunction
Dead Pear-Ox
ALD is characterized by peroxisomal dysfunction. Mutations in ABCD1 lead to the inability to transport very-long-chain fatty acids (VLCFAs) into the peroxisomes, preventing beta-oxidation and degradation.

ABCD1 Mutation
ABCD Checklist (1) Wand Mutant
ALD is caused by a mutation in the ABCD1 gene, which usually codes for a peroxisomal transmembrane protein, the ABCD1 protein, also known as the ALDP. This protein is part of the ATP-binding cassette transport family and is in charge of transporting VLCFAs into the peroxisome for degradation. Mutations in ABCD1 lead to abnormal VLCFA metabolism and accumulation within the cell.

Presentation

Adrenal Insufficiency
Damaged Adrenal Gland
Primary adrenal insufficiency (PAI) may be the first manifestation of adrenoleukodystrophy in approximately 30-40% of patients. A small percentage of patients present with isolated adrenal insufficiency, but most will continue to develop adrenomyeloneuropathy. Signs and symptoms include fatigue, gastrointestinal symptoms, myalgias, weakness, and hyperpigmentation. Clinical manifestations of adrenal involvement usually begin by 5-7 years of age.

Leukoencephalopathy
Luke's Altered Brain
Leukoencephalopathy refers to the cerebral form of ALD and reflects inflammatory cerebral demyelination. Childhood cerebral ALD corresponds to approximately 35% of ALD cases and most commonly presents between 3 and 10 years of age. Boys may initially present with learning disabilities and behavioral problems. As the disease progresses, patients may present with increasing cognitive involvement, blindness, and quadriparesis. Approximately 20% of patients with the childhood cerebral form may develop seizures.

Testicular Insufficiency
Scared Testicles
Affected males with ALD may present with clinical or subclinical hypogonadism due to VLCFA accumulation and toxicity in the Leydig cells.

Diagnosis

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Increased Very Long-chain Fatty Acids (VLCFA)

Very Long Bacon Acid-Lemon

VLCFA concentration is elevated in most patients and can be measured in plasma, fibroblasts, and blood leukocytes.

Demyelination

Unraveling-myelin on neuron

Brain magnetic resonance imaging (MRI) may demonstrate inflammatory demyelination in cerebral white matter. MRI is always abnormal in symptomatic males with cerebral forms of ALD. Neuroradiological findings include deep white matter lesions that are typically bilateral and involve the occipital-parietal region and the splenium of the corpus callosum. The spinal cord can also be affected, especially in the adrenomyeloneuropathy form, and imaging findings may reveal signal abnormalities such as hyperintense areas in T2-weighted MR images.

Genetic Testing

Test Tubes and Mutant-Genes

The diagnosis of ALD is confirmed by genetic testing in which a mutation in the ABCD1 gene is demonstrated.

Treatment

Lorenzo's Oil

Lorenzo's Oil

Lorenzo’s oil is a mixture of glyceryl trioleate and glyceryl trierucate that has been used to reduce saturated VLCFAs. Although Lorenzo’s oil has proven to normalize plasma VLCFA levels, data from clinical studies have not been able to prove its effectiveness in halting the disease progression or improving symptoms.

Hematopoietic Stem Cell Transplantation

He-man Steam Cells Train-plant

Allogeneic hematopoietic stem cell transplantation (HSCT) is a treatment option for patients with early stages of cerebral ALD. HSCT can halt the cerebral demyelination when performed at an early stage.

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