

# Adrenoleukodystrophy (ALD)

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November 14, 2025

## RECOMMENDED CITATION

mohammad looti (2025). *Adrenoleukodystrophy (ALD)*. PSYCHOLOGICAL SCALES.  
Retrieved from <https://scales.arabpsychology.com/?p=25765>

## Adrenoleukodystrophy (ALD)

**Primary Disciplinary Field(s):** Genetics, Neurology

### 1. Core Definition

Adrenoleukodystrophy (ALD) is a devastating, inherited genetic disorder classified as a peroxisomal disorder. Primarily affecting males due to its X-linked nature, ALD is fundamentally characterized by the improper functioning of the protein responsible for transporting very-long-chain fatty acids (VLCFAs) into cellular organelles called peroxisomes for degradation. This biochemical failure leads to the toxic accumulation of VLCFAs in the brain, spinal cord, and adrenal glands, precipitating the progressive breakdown of the protective myelin sheath surrounding nerve cells (demyelination) and chronic deterioration of the adrenal glands (adrenal insufficiency).

The resulting neurological damage is typically irreversible, manifesting along a wide clinical spectrum. The most aggressive and life-threatening presentation is **childhood cerebral ALD (CCALD)**, which causes rapid, severe cognitive, vision, hearing, and motor decline, often leading to death or total disability within a few years if untreated. Symptoms typically present between the ages of 4 and 10. Conversely, **Adrenomyeloneuropathy (AMN)** represents a milder, adult-onset presentation, marked primarily by progressive stiffness and weakness in the lower limbs, often coupled with bladder and bowel dysfunction. Adrenal insufficiency, also known as Addison's disease, can occur independently or alongside either neurological manifestation, highlighting the systemic nature of the disorder.

### 2. Etymology and Historical Development

The descriptive name "Adrenoleukodystrophy" encapsulates the primary tissues affected by the pathology. The prefix "Adreno-" refers to the frequent involvement of the adrenal glands; "leuko-" references the white matter of the brain, where the myelin sheath is located; and "dystrophy" signifies the abnormal degeneration or development of these tissues. The initial medical description of the syndrome is credited to Siemerling and Creutzfeldt in 1923, though they lacked the tools to identify the underlying cause, classifying it then based only on clinical and post-mortem findings.

A crucial turning point in understanding ALD occurred in the 1970s when researchers identified the accumulating **very-long-chain fatty acids (VLCFAs)** as the definitive biochemical hallmark of the condition. This discovery provided the foundation for developing reliable diagnostic tests based on blood chemistry. The genetic defect was finally pinpointed in 1993 with the identification of the causative **ABCD1 gene** (ATP-binding cassette subfamily D member 1). This gene encodes a peroxisomal membrane protein (ALDP) essential for transporting VLCFAs. The identification of the

ABCD1 mutation confirmed ALD as an X-linked genetic disorder, enabling widespread genetic testing, prenatal diagnosis, and comprehensive family counseling for at-risk populations.

### 3. Key Characteristics

**X-Linked Genetic Inheritance:** ALD is an X-linked recessive disorder, meaning the causative **ABCD1** gene resides on the X chromosome. Males, possessing only one X chromosome, lack a functional backup allele and are thus overwhelmingly susceptible to the severe manifestations of the disease. While females are typically carriers, they are not immune; due to mechanisms such as skewed X-inactivation, a significant proportion of carriers may develop neurological symptoms later in life, usually presenting as the milder AMN phenotype.

**Progressive Demyelination:** The core neurological characteristic is the chronic and progressive destruction of the myelin sheath in the brain and spinal cord. The excess VLCFAs accumulate in the glial cells (astrocytes and microglia), triggering an inflammatory response that ultimately targets and destroys myelin. Since myelin is essential for rapid and efficient communication along nerve axons, its destruction directly causes the profound neurological dysfunction, disability, and sensory loss seen in the cerebral forms of ALD. The location and rate of demyelination dictate the clinical presentation.

**Adrenocortical Dysfunction:** ALD often includes compromised function of the adrenal glands, resulting in **adrenal insufficiency** (Addison's disease). The glands fail to produce adequate levels of essential hormones, particularly cortisol and aldosterone. Symptoms can include persistent fatigue, unexplained weight loss, nausea, vomiting, and dangerously low blood pressure (hypotension). Crucially, adrenal insufficiency can precede neurological symptoms by many years or even present as the only initial symptom, underscoring the necessity of early endocrine evaluation in all diagnosed individuals.

### 4. Significance and Impact

ALD is recognized as a significant public health concern due to the high likelihood of severe neurological disability and premature mortality, particularly associated with the childhood cerebral form. The rapid and devastating trajectory of CCALD emphasizes the critical importance of timely intervention to salvage neurological function.

The understanding of the ABCD1 deficiency and the role of VLCFAs has revolutionized management strategies. The most impactful intervention has been the implementation of universal **newborn screening programs** for ALD in many regions. Early detection, often before the commencement of symptomatic demyelination, provides the only viable window for effective treatment. For children detected through screening, **Hematopoietic Stem Cell Transplantation (HSCT)** has been established as the standard of care. HSCT works by replacing the defective

blood-forming cells with healthy donor cells that can properly metabolize VLCFAs, effectively halting or slowing the progression of cerebral demyelination if performed in the very early stages of the disease.

## 5. Debates and Criticisms

Despite major therapeutic advancements, the management of ALD remains fraught with challenges and continuing debates. A primary difficulty lies in the high clinical heterogeneity of the disorder; individuals with the identical ABCD1 mutation can exhibit vastly different phenotypes, ranging from asymptomatic adulthood to rapid, devastating childhood onset. This variability makes effective prognosis and timely treatment planning complex, as clinicians must determine the precise moment to intervene with aggressive therapies.

The utility of dietary intervention, particularly **Lorenzo's oil** (a specifically formulated mixture of glyceryl trioleate and glyceryl trierucate), remains highly controversial. While this oil is undeniably effective at lowering circulating VLCFA levels in the blood, clinical trials have not definitively proven its efficacy in preventing neurological decline in all patient groups, especially once demyelination has begun. Therefore, while often used as a supplementary treatment, it is not considered a substitute for definitive therapies like HSCT.

Furthermore, HSCT itself carries inherent risks, including mortality and morbidity associated with the conditioning regimen. Deciding on the optimal timing for transplantation is critical and challenging, requiring a difficult balance between the risks of the procedure and the certainty of devastating neurological progression if left untreated. Finally, current research into **gene therapy** protocols offers immense promise by aiming to correct the underlying genetic defect, but the long-term safety profiles, durability of the therapeutic effect, and potential late-onset side effects continue to be the subject of rigorous ongoing clinical evaluation.

## Further Reading

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