It Might Be ALD

Recognizing Adrenoleukodystrophy in Adults

Adrenoleukodystrophy (ALD) is a rare, X-linked metabolic disease caused by genetic variants in the *ABCD1* gene that impair breakdown of very long-chain fatty acids (VLCFAs). In adults, it most often presents as adrenomyeloneuropathy (AMN), a slowly progressive myelopathy. Both males and females with ALD can exhibit myelopathy symptoms. In males, adrenal insufficiency may be the first or only sign for years and can be life-threatening if unrecognized — yet it is readily treated once diagnosed. Based on known incidence, many adults are living with ALD without an accurate diagnosis.

1 in 15,000
PEOPLE WORLDWIDE

AMN
MOST COMMON ADULT FORM

Up to 90%
OF WOMEN BECOME SYMPTOMATIC

WHEN TO CONSIDER ALD

Adults with ALD often end up seeing endocrinology and neurology for what are perceived as two separate issues. Considering the entire clinical picture of an individual patient is crucial in recognizing ALD. Consider testing for ALD or referring to genetics if you encounter an individual with the following features:

Primary adrenal insufficiency: ALD is an under-recognized genetic cause of primary adrenal insufficiency, particularly in males. Consider it in any male with Addison's disease — especially when 21-hydroxylase and other adrenal autoantibodies are negative — as adrenal insufficiency may precede neurological signs by years.

Progressive myelopathy: ALD is an important and frequently overlooked genetic cause of adult-onset spastic paraparesis with sensory ataxia in both males and females. Consider it in unexplained chronic progressive myelopathy — leg stiffness and weakness, gait and balance impairment, with bladder, bowel, or sexual dysfunction — including cases provisionally labeled hereditary spastic paraplegia.

Family history: Any individual with family history of ALD, male or female, should undergo a workup for ALD if they are at risk to have inherited the familial variant.

Most patients have no known family history of ALD — its absence should not lower suspicion.

For informational purposes only. This document is intended to describe common clinical considerations, but may not be appropriate for every patient or case. Decisions surrounding patient care depend on the physician's professional judgement in consideration of all available information for the individual case.

THE ADULT PRESENTATIONS

Adrenomyeloneuropathy (AMN): The most common adult form, typically beginning between the 20s and 40s in men. It can present as slowly progressive leg stiffness and weakness, impaired balance and sensation, and sphincter dysfunction.

Adrenal insufficiency: Up to about 80% of affected males develop primary adrenal insufficiency, often before any neurological signs, appearing as fatigue, weight loss, salt craving, hyperpigmentation, or an adrenal crisis. Adrenal function should be assessed at diagnosis and monitored over time. AI most often appears during childhood in males with ALD, but can also begin in adulthood. Continued monitoring is critical in adult males with ALD even in the absence of known adrenal insufficiency.

Cerebral ALD (cALD): A substantial portion of males with AMN will go on to develop cerebral disease, a rapidly progressive loss of myelin in the brain that can initially present with behavioral changes. Symptoms are progressive and eventually lead to loss of abilities and death if not treated. Although cerebral ALD is most commonly diagnosed in boys, it is now recognized that adult men remain at risk for cALD and continued monitoring is critical even in the absence of symptoms.

Symptomatic women with ALD: Women are not merely unaffected carriers: up to 90% develop symptoms in their lifetime — a myelopathy resembling AMN, typically beginning in the 30s or 40s, though onset varies widely. Cerebral disease and adrenal insufficiency are rare in women. Because about 15% of affected women have normal VLCFA levels, *ABCD1* genetic testing — the diagnostic gold standard — is preferred in females. Care is supportive and often spans neurology, urology, physical therapy, and pain management.

WHY AN ACCURATE DIAGNOSIS MATTERS

Adrenal insufficiency is treatable with hormone replacement, and recognizing it prevents life-threatening adrenal crisis. A confirmed diagnosis also enables cascade testing of relatives — including boys, for whom early detection of cerebral ALD and adrenal insufficiency is critical and time-sensitive. Some men with AMN who develop cerebral disease will be eligible for hematopoietic cell transplant (HCT), which halts the progression of cALD. Time is critical, as transplant does not reverse neurological damage, but can prevent progression if the disease is caught early enough and an individual is eligible for transplant. Clinical trials are available for men with AMN, and research opportunities exist for symptomatic women; there is currently no proven disease-modifying therapy for established AMN, so care is supportive alongside adrenal treatment. Males and females with ALD require a comprehensive care team. Males should always be followed by neurology and endocrinology for monitoring. Males and females may require additional specialists depending on symptoms and needs, like urology, gastroenterology, genetics, or pain management. Consider referring your patient to an ALD or leukodystrophy expert center for evaluation and management.

TESTING

Refer to genetics for a comprehensive workup for ALD. If you have a strong clinical suspicion of ALD, consider ordering the following tests while the referral is pending.

Biochemical: Very long-chain fatty acids (VLCFAs)/ Peroxisomal fatty acid profile. This test is diagnostic in males but is normal in about 15% of females with ALD, so *ABCD1* genetic testing is recommended for females, including for cascade testing.

Genetic: *ABCD1* genetic testing (the diagnostic gold standard). This can be examined as a part of single gene testing, panel testing, or comprehensive testing like exome or genome sequencing.

Neurological: If you suspect cerebral ALD, order a brain MRI to confirm. Note that interpretation of brain MRIs in males with ALD can be challenging, and images should be interpreted by neuroradiologists or clinicians with expertise in identifying cALD.

ALD AS AN INCIDENTAL DIAGNOSIS

In 2025, *ABCD1* was added to the ACMG secondary-findings list (v3.3), which is a list of actionable results returned to patients who consent to receive them during exome or genome sequencing. Some patients may therefore incidentally learn about ALD when they pursue genetic testing for other reasons. Two caveats matter:

ACMG guidance does not report a single heterozygous variant, so a woman with ALD can be missed, and variants of uncertain significance are not returned. When ALD is clinically suspected, order full *ABCD1* sequencing with deletion/duplication analysis rather than relying on secondary findings.

Other patients incidentally learn about a diagnosis of ALD during cascade testing after a relative's diagnosis. This is becoming increasingly common after a relative's newborn screen results. Regardless of the method of diagnosis or whether an individual currently presents with symptoms, males with ALD need lifelong monitoring for adrenal insufficiency and cerebral ALD.

CASCADE TESTING & FAMILY IMPLICATIONS

A single diagnosis often uncovers an extended family at risk. Offer genetic counseling and testing across generations for at-risk relatives. Each child of a woman with ALD has a 50% chance of inheriting the variant; all daughters and no sons of an affected man inherit it. Identifying at-risk boys early is the highest priority, as it opens the door to surveillance and timely treatment of the cerebral form. Discuss reproductive options, including IVF with preimplantation genetic testing, where appropriate. Refer newly diagnosed patients to genetics for a comprehensive evaluation and counseling.

References & Resources:

1. Engelen M, et al. International Recommendations for the Diagnosis and Management of Patients With Adrenoleukodystrophy. Neurology. 2022;99(21):940–951. PMID 36175155.

2. Engelen M, et al. X-linked adrenoleukodystrophy in women: a cross-sectional cohort study. Brain. 2014;137(3):693–706. PMID 24480483.

3. Lee K, et al. ACMG SF v3.3 list for reporting of secondary findings in clinical exome and genome sequencing. Genet Med. 2025. PMID 40568962.

4. U.S. FDA. Skysona (elivaldogene autotemcel) prescribing information and safety labeling changes; 2025.

In this resource, "female"/"women" and "male"/"men" refer to individuals with XX and XY chromosomes, respectively. Individuals with XY chromosomes remain at risk for adrenal insufficiency and cerebral ALD and should be screened regardless of gender identity. Content adapted from ALD Connect resources and the 2022 international consensus recommendations.