It Might Be ALD

Recognizing Adrenoleukodystrophy in Children

Adrenoleukodystrophy (ALD) is a rare, X-linked metabolic disease caused by genetic variants in the *ABCD1* gene. The defective protein impairs breakdown of very long-chain fatty acids (VLCFAs), which accumulate in the adrenal cortex, spinal cord, and cerebral white matter.

1 in 15,000
PEOPLE WORLDWIDE

~40%
OF BOYS DEVELOP CEREBRAL ALD

3–12 yrs
TYPICAL ONSET OF CEREBRAL ALD

In boys, ALD can cause two life-threatening conditions: primary adrenal insufficiency and childhood cerebral ALD, a rapidly progressive loss of myelin in the brain. Both are treatable, but only when caught early, which makes prompt recognition critical. Newborn screening now identifies many affected boys before symptoms begin, however older children or adults, or those from certain states, may not have been screened for ALD at birth. Girls with ALD are not expected to develop symptoms in childhood because of the X-linked nature of the condition.

WHEN TO CONSIDER ALD IN A CHILD

Boys 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 a male with the following features:

Primary adrenal insufficiency: ALD is a leading genetic cause of primary adrenal insufficiency in boys, and it may be the first sign of the condition — sometimes years before any neurological change. Consider it in any boy with Addison's disease, particularly when 21-hydroxylase and other adrenal autoantibodies are negative.

Neurocognitive or behavioral decline: The childhood cerebral form often begins as falling school performance or new attention and behavior problems — easily mistaken for ADHD or a learning disability — soon followed by deficits in vision, hearing, gait, or coordination. Consider ALD in a school-age boy with progressive decline or loss of previously acquired skills.

Brain MRI: Suggestive of leukodystrophy.

An affected relative: Any boy with a maternal family history of ALD, unexplained Addison's disease, or progressive myelopathy warrants testing, regardless of symptoms.

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

WHY EARLY DIAGNOSIS MATTERS

Childhood cerebral ALD can be halted with hematopoietic cell transplant (HCT) (or, in selected boys, gene therapy) — but only when treatment begins early, while MRI changes are minimal and the child is still neurologically intact. Treatment stabilizes disease; it does not reverse damage already done, so the window is narrow. Adrenal insufficiency is treatable with hormone replacement, and recognizing it prevents fatal adrenal crisis. A confirmed diagnosis also enables structured neurological and adrenal monitoring so treatment can start at the first sign, plus cascade testing of at-risk relatives.

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. *ABCD1* is now included on secondary findings for exome and genome sequencing, so may be incidentally identified if broader testing is ordered.

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

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.

RECOMMENDED MONITORING IN DIAGNOSED BOYS

Once a diagnosis is made, refer boys with ALD to endocrinology, neurology, and genetics. Consider referring your patient to an ALD or leukodystrophy expert center for evaluation and management. International recommendations for diagnosis and management of patients with ALD are available and should be consulted if an individual is diagnosed with ALD[1]. Because cerebral conversion and timing of adrenal insufficiency is unpredictable, boys identified by screening or family testing are followed on a surveillance schedule so that the disease is caught at a treatable stage. ALD is life threatening, and identification of ALD and adherence to recommended monitoring allows for prompt, life-saving treatment.

Manifestation	Screening / Diagnostic Tool	Screening Protocol
Cerebral ALD	MRI	2 yr, baseline scan; 2–12 yr, every 6 months; >12 yr, yearly
Adrenal Insufficiency	Morning fasted cortisol, ACTH, renin, electrolytes	0–6 m, start screening; 6 m–10 yr, every 3–6 months; >10 yr, yearly

Routine monitoring for cALD and AI is not recommended in females in the absence of symptoms, as these phenotypes are very rare in females.

GENETICS & DISEASE MECHANISM

ALD is caused by pathogenic variants in ***ABCD1*** on the X chromosome, which encodes a peroxisomal transporter (ALDP). Loss of function impairs breakdown of VLCFAs, which accumulate and are toxic to the adrenal cortex, spinal cord, and cerebral white matter. There is no reliable genotype-phenotype correlation — the same variant can cause different phenotypes even within one family — so ongoing monitoring, rather than one-time risk prediction, is central to care.

TREATMENT

Consider referring your patient to an ALD or leukodystrophy expert center for evaluation and management.

Cerebral ALD: Allogeneic hematopoietic cell transplant (HCT) is the established treatment and is most effective performed early — while demyelination is limited (low Loes score, typically ≤ 9) and neurological function is intact; it stabilizes rather than reverses disease. Gene therapy (elivaldogene autotemcel, *Skysona*) is FDA-approved for boys 4–17 with early, active cerebral ALD, but carries a boxed warning for hematologic malignancy and is now indicated only for boys who lack a suitable matched donor.

Adrenal insufficiency: Managed with glucocorticoid (and, if needed, mineralocorticoid) replacement, plus stress-dosing education and an emergency plan to prevent life-threatening adrenal crisis. Treatment is lifelong and requires monitoring by endocrinology.

NEWBORN SCREENING & FAMILY TESTING

ALD was added to the U.S. Recommended Uniform Screening Panel (RUSP) in 2016 and is now part of the newborn screen in most states. Screening identifies affected boys presymptomatically, enabling the monitoring that allows cerebral disease and adrenal insufficiency to be treated before irreversible harm. A positive screen is confirmed with VLCFA and *ABCD1* testing. A confirmed diagnosis should prompt cascade testing across the family. Coverage varies by state, so an older, unscreened child is common and clinical suspicion still matters.

References and Resources:

1. Engelen, M., et al. (2022). International Recommendations for the Diagnosis and Management of Patients With Adrenoleukodystrophy: A Consensus-Based Approach. Neurology, 99(21), 940–951. https://doi.org/10.1212/WNL.0000000000201374. PMID: 36175155.

Treatment of ALD can have time-sensitive implications. Working with a specialist knowledgeable about ALD diagnosis and treatment is important. Please contact info@aldconnect.org to be connected to an ALD expert.