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Early Diagnosis, Vigilant Monitoring

Recognizing and managing adrenoleukodystrophy (ALD)

> When we identify a child with adrenal insufficiency, one of the first things that we should think about is ALD, if that child is a boy.

BRADLEY MILLER, MD, PhD
Pediatric endocrinologist

Patients are actor portrayals.
Physician is a pediatric endocrinologist.

An early diagnosis of ALD can save lives[1]

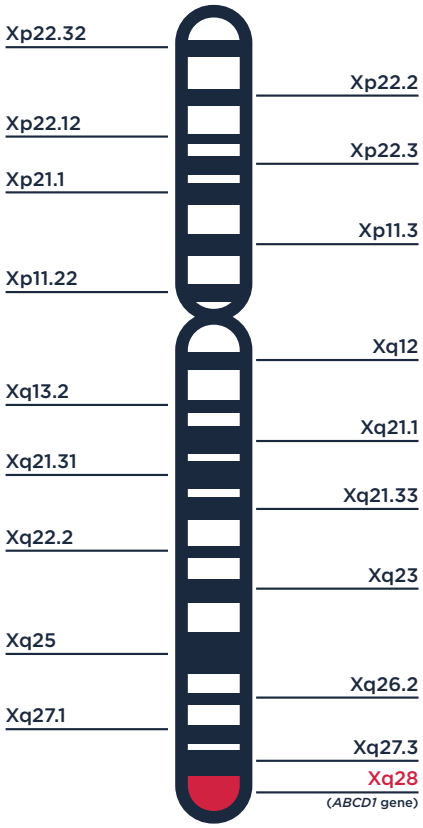
Know how to recognize and manage patients who may have ALD

As part of the initial evaluation of preadolescent boys with primary adrenal insufficiency, the Endocrine Society Clinical Practice Guidelines recommend screening for elevated very long-chain fatty acid (VLCFA) levels in plasma in order to detect the possibility of adrenoleukodystrophy (ALD),[2] which may be further confirmed through genetic testing.

ALD is a rare genetic disease that can progress to a serious and life-threatening condition[3,4]

ALD is an X-linked genetic disease affecting approximately 1:21,000 males[3]

- Although ALD primarily affects males, it is possible for females to develop symptoms of the disease in late adulthood[5]
- ALD has been reported in all racial and ethnic backgrounds[5]
- ALD consists of a spectrum of phenotypes, which may overlap throughout the lifetime of a patient[1]



The underlying cause of ALD is a genetic mutation[5]

ALD is caused by mutations in the *ABCD1* gene that result in deficiency of the peroxisomal protein ALDP. This leads to accumulation of VLCFAs in plasma and tissue—primarily of the nervous system and adrenal glands.[5]

Even among members of the same family, it is currently not possible to predict the future phenotype of a boy with ALD without monitoring.[3,5]

Identifying and managing ALD

In order to diagnose and address ALD in your patients with adrenal insufficiency, remember these 3 steps:

1 RECOGNIZE

2 MEASURE

3 CONSULT

On the next few pages, we will review the details of these steps.

1 RECOGNIZE THE LINK

Adrenal insufficiency is often the first symptom of ALD[2]

Symptoms are associated with other conditions, like Addison's disease or other causes of adrenal insufficiency, creating difficulty in diagnosis.[6]

80% to 86% of boys diagnosed with ALD also have adrenal insufficiency[7]

While adrenal insufficiency can initially present as early as 5 months of age, on average patients are **4 to 5 years** of age at presentation[7]

SYMPTOMS ASSOCIATED WITH ADRENAL INSUFFICIENCY INCLUDE[2]:

- Fatigue
- Loss of appetite
- Skin bronzing
- Abdominal pain

2 MEASURE VLCFA LEVELS IN PLASMA

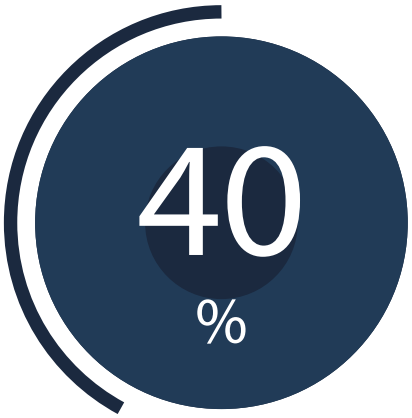
Early detection is possible, as increased levels of plasma VLCFAs are indicative of ALD[8]

The Endocrine Society Clinical Practice Guidelines recommend measuring VLCFA levels in plasma in order to diagnose ALD as part of the evaluation of preadolescent boys with primary adrenal insufficiency.[2]

Endocrinologists may have the opportunity to identify the first signs of ALD. An early diagnosis of ALD could save a life.[1,2]

3 CONSULT WITH AN ALD SPECIALIST

If you confirm ALD, consult with and refer the patient to an ALD specialist for the best possible outcomes[1]



About 40% of boys with ALD develop a severe, progressive, and life-threatening neurodegenerative form of the disease known as cerebral ALD[4,8]

In most patients, cerebral ALD is a rapidly progressing disease that causes progressive behavioral, cognitive, and neurologic deficits and total disability followed by death within 5 years after onset of symptoms.[8,9]

A neurologist with expertise in ALD or another ALD specialist partner can identify changes in the brain that are indicative of progression to cerebral ALD.[1]

Vigilant monitoring of patients with ALD can help to identify and address progression to cerebral ALD.[1,8]

Cerebral ALD involves the destruction of the myelin sheath that protects nerve cells in the brain. If left undiagnosed and untreated, progression of cerebral ALD is rapid, causing **severe loss of neurologic functions** including loss of cognition, vision, hearing, and motor function. Usually, untreated cerebral ALD results in death.[8]

- **White matter changes on MRI** precede the onset of symptoms, so **MRI monitoring is critical** as it can detect progression to cerebral ALD **before any symptoms arise**[1]
- **Symptoms of progression** to cerebral ALD may **mimic conditions like attention-deficit/hyperactivity disorder (ADHD)**, autism, or other home and school problems, which can delay diagnosis[5]

Roles of the ALD care team

A **neurologist** who specializes in ALD can provide[1]:

- Regular magnetic resonance imaging (MRI) to monitor for changes in the brain indicative of cerebral progression
- Consultations on treatment if progression to cerebral ALD is detected
- Broader access to specialized resources that can help boys and families manage ALD

The **pediatric endocrinologist** will provide[9]:

- Regular adrenal assessments and referral to neurologist or metabolic specialist
- Ongoing management of treatment for adrenal symptoms

Regular MRI scans in boys diagnosed with ALD is critical to detect white matter changes indicative of progression of cerebral ALD[1]

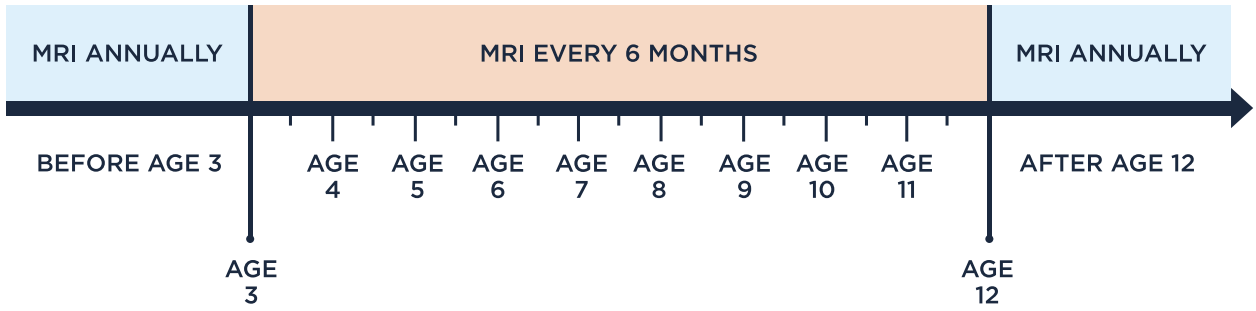
> Once we have a positive VLCFA test, then we need to make the referral to determine ALD and start monitoring.

BRADLEY MILLER, MD, PhD
Pediatric endocrinologist

A neurologist or other ALD specialist will conduct vigilant MRI monitoring to help in timely identification of life-threatening cerebral ALD[1]

Studies support MRI evaluation at the earliest possible opportunity—ideally, before symptoms of cerebral involvement appear in boys with ALD[1]

CURRENT GUIDANCE RECOMMENDS AN MRI ANNUALLY UNTIL AGE 3, **EVERY 6 MONTHS** BETWEEN AGES 3 AND 12, AND ANNUALLY THEREAFTER[10]



> Once a child has been diagnosed with ALD, it's important that they see a neurologist for screening for brain changes that are part of the disease.

BRADLEY MILLER, MD, PhD
Pediatric endocrinologist

Early diagnosis of ALD, along with regular monitoring, can help ALD specialists initiate treatment before severe and irreversible brain damage occurs.[1]


R
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SP H23.5
SL 5.0
FoV 199*220
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W 1288
C 667
TR 6300.0
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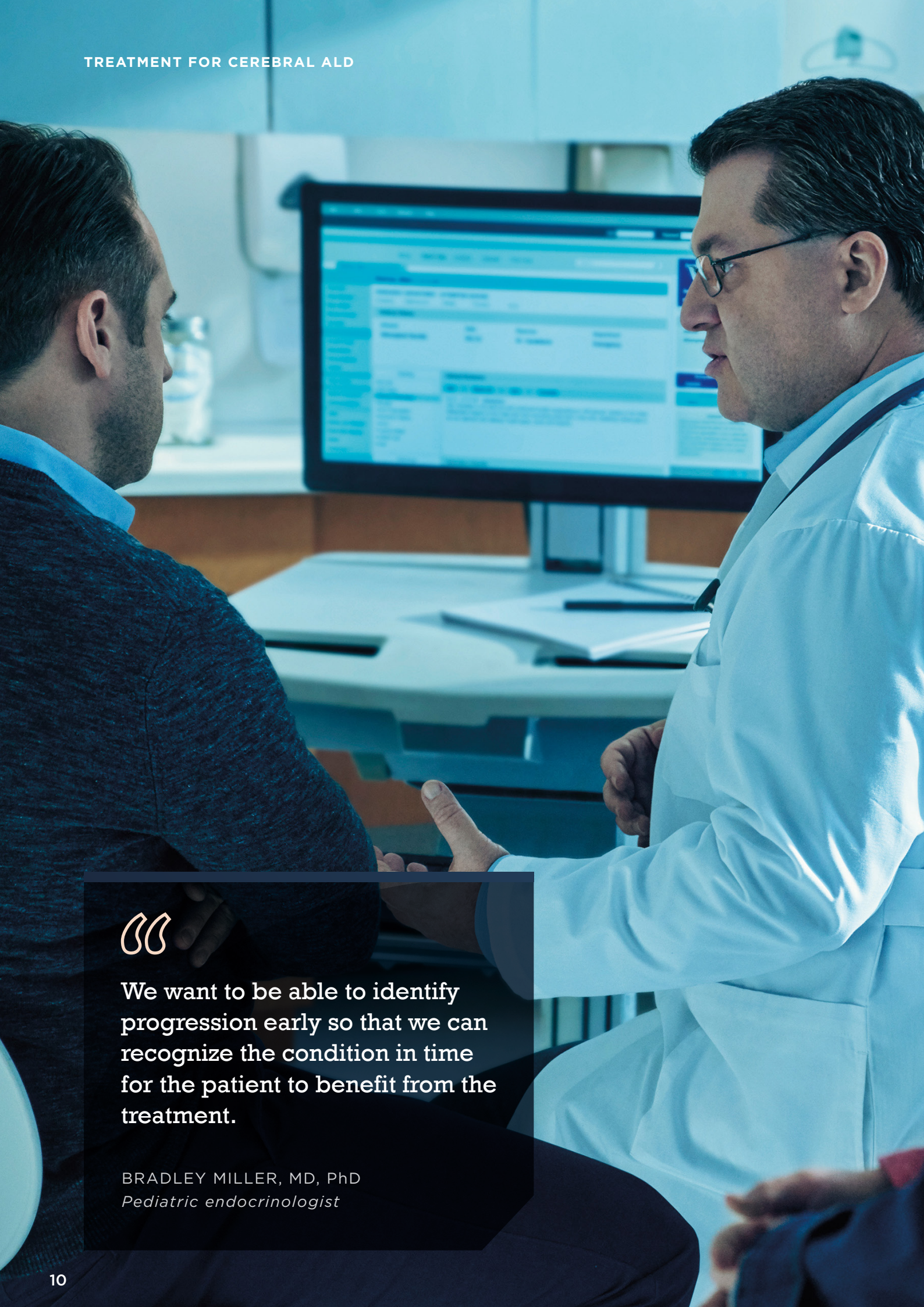

> We want to be able to identify progression early so that we can recognize the condition in time for the patient to benefit from the treatment.

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Allogeneic hematopoietic stem cell transplantation (allo-HSCT) can be lifesaving and is currently the only treatment for cerebral ALD that can arrest disease progression[4]

Early diagnosis during the first signs of cerebral involvement is critical because outcomes with allo-HSCT are more favorable with earlier initiation of treatment[1]

In a study of patients with both early and advanced cerebral ALD, treatment in early disease demonstrated greater major functional disability (MFD)–free survival (survival without experiencing any MFDs) and overall survival[11]

	MFD-FREE SURVIVAL		OVERALL SURVIVAL
	2 YEARS	5 YEARS	
Early Disease (n=27)	91%	76%	94%
Advanced Disease (n=10)	20%	10%	90%

MFD-free survival is important to measure in cerebral ALD—preventing the loss of life does not equate to the preservation of neurologic function and quality of life. In this study, **MFDs include**[11]

- Loss of communication
- Cortical blindness
- Tube feeding dependence
- Wheelchair dependence
- Complete loss of voluntary movement
- Death related to neurologic deterioration

Also important to note is the type of donor providing stem cells. Outcomes of allo-HSCT are more favorable with stem cells from a matched sibling donor compared to cells from a mismatched or unrelated donor.[11]

≤30% of boys with cerebral ALD have a matched sibling donor available for allo-HSCT.[4]

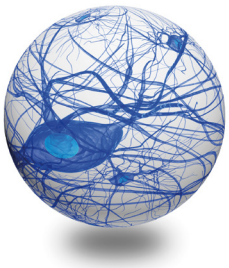
Early diagnosis and treatment of cerebral ALD demonstrates better overall outcomes[1]

Advocacy organizations support clinicians and provide resources for patients and caregivers

Clinicians can help families of children diagnosed with ALD or cerebral ALD find additional support by connecting them to patient organizations, including advocacy groups.

ALDConnect

aldconnect.org



GLOBAL LEUKODYSTROPHY INITIATIVE

theglia.org

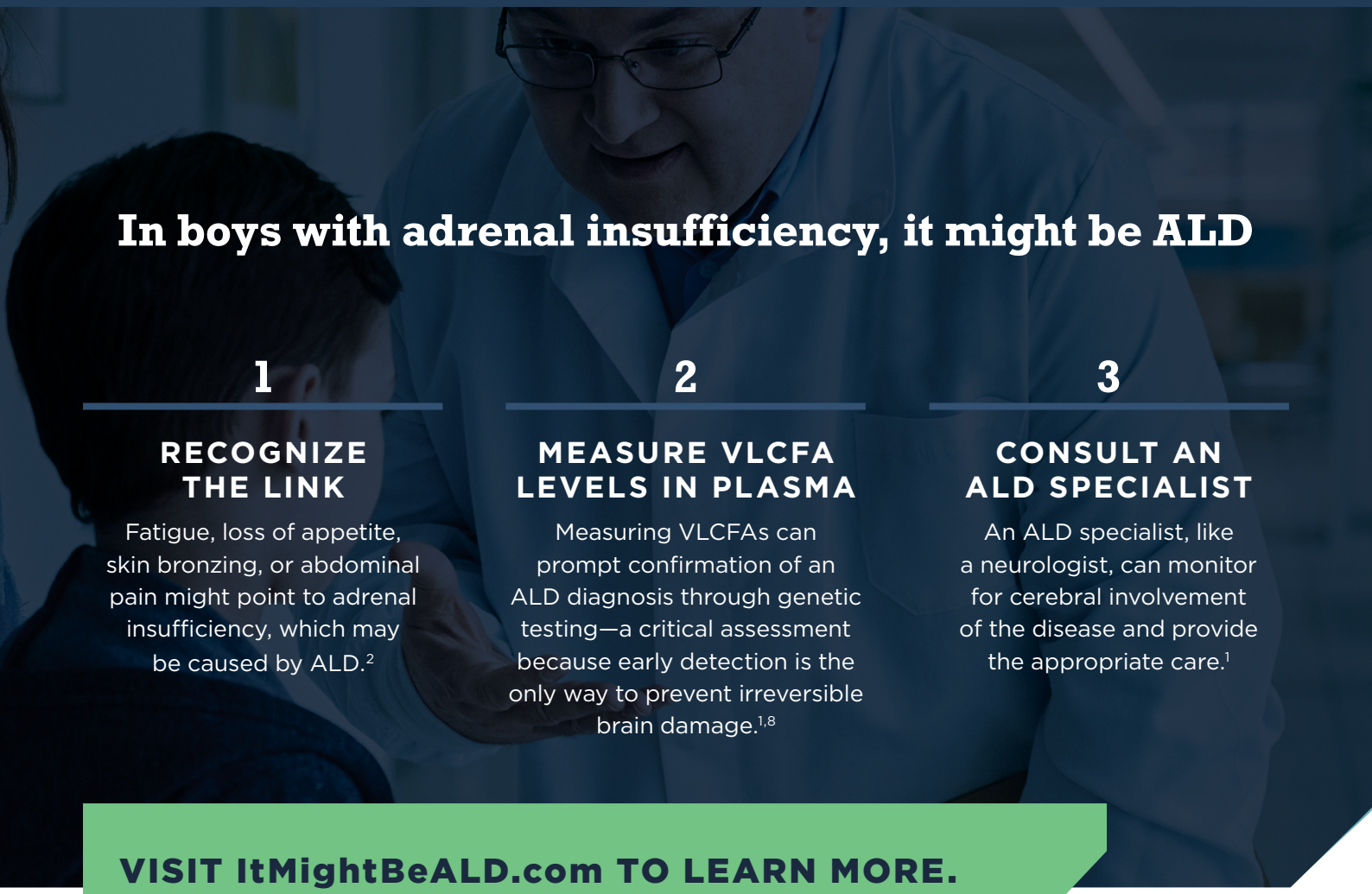
WORLD Leukodystrophy ALLIANCE

leukodystrophyalliance.org

These organizations provide education and support to those whose lives are affected by ALD—their work is crucial and commendable.

This list is provided for reference only and is not intended as a comprehensive list of resources.

There are organizations that are here to help.
For more information, visit ItMightBeALD.com



In boys with adrenal insufficiency, it might be ALD

1

RECOGNIZE THE LINK

Fatigue, loss of appetite, skin bronzing, or abdominal pain might point to adrenal insufficiency, which may be caused by ALD.[2]

2

MEASURE VLCFA LEVELS IN PLASMA

Measuring VLCFAs can prompt confirmation of an ALD diagnosis through genetic testing—a critical assessment because early detection is the only way to prevent irreversible brain damage.[1,8]

3

CONSULT AN ALD SPECIALIST

An ALD specialist, like a neurologist, can monitor for cerebral involvement of the disease and provide the appropriate care.[1]

VISIT ItMightBeALD.com TO LEARN MORE.

References: 1. Moser HW, Mahmood A, Raymond GV. X-linked adrenoleukodystrophy. *Nat Clin Pract Neurol.* 2007;3(3):140-151. **2.** Bornstein SR, Allolio B, Arlt W, et al. Diagnosis and treatment of primary adrenal insuffiency: an Endocrine Society clinical practice guideline. *J Clin Endo Metab.* 2016;101(2):364-389. **3.** Bezman L, Moser AB, Raymond GV, et al. Adrenoleukodystrophy: incidence, new mutation rate, and results of extended family screening. *Ann Neurol.* 2001;49:512-517. **4.** Miller WP, Rothman SM, Nascene D, et al. Outcomes after allogenic hematopoietic cell transplantation for childhood cerebral adrenoleukodystrophy: the largest single-institution cohort report. *Blood.* 2011;118(7):1171-1178. **5.** Kemp S, Huffnagel I, Linthorst GE, Wanders RJ, Engelen M. Adrenoleukodystrophy – neuroendocrine pathogenesis and redefinition of natural history. *Nat Rev Endocrinol.* 2016;12(10):606-615. **6.** Laureti S, Casucci G, Santeusanio F, Angeletti G, Aubourg P, Brunetti P. X-linked adrenoleukodystrophy is a frequent cause of idiopathic Addison's disease in young adult male patients. *J Clin Endocrinol Metab.* 1996;81(2):470-474. **7.** Dubey P, Raymond GV, Moser AB, et al. Adrenal insufficiency in asymptomatic adrenoleukodystrophy patients identified by very long-chain fatty acid screening. *J Pediatr.* 2005;146(4):528-532. doi:10.1016/j.jpeds.2004.10.067. **8.** Engelen M, Kemp S, Poll-The B-T. X-linked adrenoleukodystrophy: pathogenesis and treatment. *Curr Neurol Neurosci Rep.* 2014;14(486):1-8. **9.** Mahmood A, Dubey P, Moser HW, Moser A. X-linked adrenoleukodystrophy: therapeutic approaches to distinct phenotypes. *Pediatr Transplant.* 2005;9(suppl 7):55-62. **10.** Engelen M, Kemp S, de Visser M, et al. X-linked adrenoleukodystrophy (X-ALD): clinical presentation and guidelines for diagnosis, follow-up and management. *Orphanet J Rare Dis.* 2012;7:51. **11.** Raymond GV, Aubourg P, Paker A, et al. Survival and functional outcomes in boys with cerebral adrenoleukodystrophy with and without hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant.* 2019;25(3):538-548. doi: 10.1016/j.bbmt.2018.09.036.

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