



### Avoiding the Misdiagnosis of Adrenoleukodystrophy: Distinguishing ALD from ADD/ADHD

*From data reported in recent peer-reviewed literature*

***In diagnosis, one letter in the alphabet can make a life-saving difference. Adrenoleukodystrophy (ALD), while a rare disorder, is important for clinicians to keep on their radar screen since it is typically fatal though amenable to treatment in its earlier stages. Prompt and accurate recognition, therefore, is critical—particularly differentiating it from other causes of behavioral disturbances in boys. Because the behavioral problems that accompany ALD are also common among non-affected boys, ALD is frequently misdiagnosed, most often as attention-deficit disorder (ADD) or attention-deficit hyperactivity disorder (ADHD). In a culture that is increasingly attuned to ADD, clinicians should keep the differential diagnoses in mind as well. Those involved in the assessment of children with learning or attention problems should be alert to and regularly screen for certain signs and symptoms suggestive of ALD, a life-threatening, often fatal condition. Very early recognition of ALD not only offers these patients their only chance for treatment, it also initiates the process of family screening sooner rather than later, a critical component in the management of this disorder. For instance in a study further described in this report, the diagnosis of ADHD and treatment with stimulant medication appeared to be appropriate in a 9-year-old boy until his decline 2 years later. The boy's inattention, agitation, learning problems, impulsivity and noncompliant behavior were rightly considered to be characteristic of ADHD—though these behaviors can also accompany ALD. Misdiagnosis unnecessarily delayed the appropriate treatment, and likely robbed this child of his best possible prognosis.***

#### **ALD Phenotypes**

ALD is an X-linked recessive metabolic disorder characterized by progressive neurologic deterioration due to cerebral white matter demyelination, along with adrenal insufficiency. A recent study estimates the minimum incidence of ALD to be one in 17,000 (Bezman L, Moser AB, Raymond GV et al. *Ann Neurol.* 2001;49:512-517), a figure that is consistent across all racial, ethnic, and geographic backgrounds. A common form of ALD is childhood cerebral ALD, which usually emerges in previously healthy boys aged 5 to 10 and is often heralded by behavioral problems or school difficulties. The phenotypic expression of ALD varies widely, even among affected members of the same family, from the rapidly progressive childhood cerebral form to the later-onset and more slowly progressive adrenomyeloneuropathy (AMN). It is not possible to predict the future phenotype in an asymptomatic boy or affected fetus.

The classification of ALD is based on the age of onset and the principal site of the central nervous system (CNS) lesions. The most common phenotype, the cerebral demyelinating form, affects previously healthy boys aged 5 to 10 years and represents approximately 45% of all ALD cases. It is characterized by an inflammatory process that destroys the myelin, causing relentless progressive deterioration to a vegetative state, usually within 5 years. Most of the remaining cases occur as the adult form, AMN. This phenotype affects the spinal cord and, to a lesser degree, the peripheral nerves, with minimal or no inflammatory lesions, although about one third of these adult men will at some point experience cerebral involvement. Adrenocortical insufficiency (Addison's disease) is seen in almost all patients with ALD, at some phase of the illness. Any male patient with adrenocortical insufficiency should be screened for ALD.

#### **Neurobiology of ALD**

The pathogenesis of ALD has not been clearly delineated. The biochemical abnormality is an accumulation of saturated very-long-chain fatty acids (VLCFA) in the serum and tissues. The VLCFA storage in the CNS is associated with an inflammatory response that is partly responsible for the demyelination. The relationship between VLCFA accumulation, brain inflammatory response and pathogenesis of the disease remains unclear. The ALD gene has been mapped to chromosome Xq28, with over 665 mutations currently identified. The gene encodes a peroxisomal membrane protein—labeled ALD protein—that is a member of the ATP-binding-cassette (ABC) transporter family. The ALD protein is essential in tissues such as myelinated tracts and the adrenal gland. The phenotypic variation is not associated with the severity of the biochemical defect or the nature of the genetic mutation, suggesting that modifier genes or epigenetic factors may modulate disease severity.

“No matter what mutation is responsible, there is absolutely no way to predict which version of this disease a person will have, whether it is the type that will take the life of a 10-year-old, or the type that will lead to some degree of disability later in life. Even identical twins with the same gene mutation can have two completely different disease presentations,” according to Rachel Salzman, DVM, Chief Scientific Officer for the Stop ALD Foundation.

#### **Psychosocial Manifestations of ALD in Children**

The early identification of ALD is challenging because the earliest presenting symptoms may seem nonspecific, or overlapping with numerous other medical conditions and psychiatric or developmental disorders of childhood. In a large percentage of children with ALD, behavioral manifestations and school difficulties are the initial findings; therefore, the potential for misdiagnosis is significant (Moser HW, Smith KD, Moser AB: X-linked adrenoleukodystrophy, Scriver CR, Beaudet AL, Sly WS, Valle D (eds): *The Metabolic and Molecular Basis of Inherited Diseases*, 7<sup>th</sup> ed. New York, NY, McGraw Hill, 1995, pp 2325-2349). Cognitive impairments in ALD may involve an impaired capacity to sustain attention, and impairments in spatial and visuo-motor coordination which lead to learning disabilities.

“When the lesions are located in the frontal lobes, planning, executive reasoning, and attention deficits are often the symptoms that lead to misdiagnosis as ADD/ADHD,” according to Patrick Aubourg, MD, of the Hospital Saint-Vincent de Paul, Paris, France. Patients with occipital involvement may also have similar, albeit less marked symptoms, due to disconnection between occipito-parietal and frontal lobes. “Misdiagnosis is most common when demyelination occurs in the frontal lobe. Frontal lobe cognitive dysfunction can lead to difficulties at school, which are recognized by teachers and parents. This is actually most common after the age of 10,” said Dr. Aubourg.

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According to Hugo Moser, MD, University Professor of Neurology and Pediatrics, Johns Hopkins University and the Kennedy Krieger Institute, Baltimore, Maryland, “ALD has often been misdiagnosed as epilepsy, psychosis, Asperger Syndrome (a form of autism), other genetic disorders such as Batten disease, and brain tumors, often after exploratory surgery has been performed.” These disorders are also part of the differential diagnosis.

In addition to the characteristic psychosocial manifestations, certain physical signs may alert the clinician. Visual impairment caused by involvement in the optic tracts is frequently found at an early stage and misdiagnosed. Motor symptoms at an advanced stage may include gait disturbances, poor handwriting, and speech difficulties. Overt physical symptoms such as seizures, cortical deafness, and difficulty swallowing may be observed in later stages but in their more subtle forms may be picked up by the astute clinician (ie, early hearing loss can manifest as difficulty in locating sounds, loss of startle reflex, daydreaming, difficulty with spoken language, as well as academic problems). Dr. Moser pointed out that the adult form of ALD continues to be misdiagnosed, often as multiple sclerosis, spastic paraparesis, and lumbar stenosis. “This is another factor leading to the failure to screen families in a timely manner that would identify relatives who are still asymptomatic,” he said.

### Case Reports Highlight Potential for Misdiagnosis

Two case studies reported by Ievers et al demonstrate the likelihood of misdiagnosis (Ievers CE, Brown RT, McCandless SE et al. *J Dev Behavior Pediatrics*. 1999;20(1):31-35). The report describes two patients, aged 9 and 12, who underwent extensive psychological testing. The older child had been previously diagnosed with ADHD and appeared to respond well to stimulant medication before showing a marked increase in inattention, talkativeness, activity level, and impulsivity two years later. The 9-year-old’s most striking symptoms were visual problems and learning disabilities. Both children had a family history suggestive of ALD and further testing revealed that the diagnosis for both of these boys was, indeed, ALD which was the underlying cause of all clinical and behavioral signs observed in both children.

During testing, both boys displayed significant and obvious problems with short-term memory, auditive discrimination, and/or attention that often required examiners to repeat the questions. The boys were agitated, had difficulty remaining seated, and were generally unmanageable. Both demonstrated marked impairment in adaptive behavior relative to their peers and significant impairments in reading and mathematics. Parental ratings of both boys’ behavior showed most symptoms to be associated with attention problems (ie, problems with concentration, sitting still, impulsivity, and immature behavior). In addition, the parents reported oppositional behavior, noncompliance with requests, and general emotional lability.

### Clinician’s Challenge

The distinction between degenerative disorders such as ALD and developmental or behavioral disorders such as ADHD is shown in the following table:

#### Signs and Symptoms of Degenerative vs. Developmental/Behavioral Disorders

	Degenerative Disorders (eg, ALD)	Developmental/Behavioral Disorders (eg, ADHD)
Family History	Sibling with unexplained death or neurologic abnormality (such as multiple sclerosis), or alternatively, lack of a suggestive family history; Addison’s disease	Learning disabilities, attention disorders, behavior problems often reported in family members
Disease Course	Onset or marked worsening of symptoms; preschool and early school years often normal	Behavioral/developmental symptoms chronic, often noticed when child begins school; ADHD diagnosis requires onset of symptoms before age 7
Comorbidity	Symptoms of multiple externalizing and internalizing disorders (ie, depression, anxiety) common; neurological signs such as seizures often present; adrenal insufficiency often present	Symptoms of multiple externalizing and internalizing disorders (ie, depression, anxiety) less common; adrenal insufficiency lacking

Adapted from Ievers CE, Brown RT, McCandless SE et al. *J Dev Behavior Pediatrics*. 1999;20(1):31-35.

“Patients who have cerebral ALD often develop cognitive dysfunction that can mimic ADHD, including frontal symptoms with difficulties in concentration, attention, and reasoning. It is a complicated differential, but when ADD/ADHD is diagnosed strictly on the basis of specific, formal criteria, it will be less likely to be confused with ALD,” emphasized Dr. Aubourg.

### Approach to Diagnosis

In assessing patients, the clinician should be attuned to the following:

- Family history of significant medical conditions, early morbidity, or symptoms of behavioral or developmental disorders that may appear to be genetic
- Signs of abnormal development in the child
- Change in child’s functioning, such as declines in cognition, learning, behavior, or emotional regulation; rapid acceleration of such change occurs later on
- Late onset of symptoms that typically occur earlier in childhood, such as attention or learning problems
- Visual-spatial or visual-perceptual difficulties
- Lack of sustained response to symptomatic therapies

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While a careful and detailed family history is of primary importance in assessing children referred for behavioral and developmental problems, Dr. Salzman, offered a caveat. "While virtually all cases are genetically based, inheritance may exist merely in chromosomal form. Due to the very wide phenotypic variation, taking a family history may not immediately reveal the genetic clues to the diagnosis," she noted. The initial diagnosis is often suggested by T2-weighted MRI findings in young boys being observed for progressive behavioral change. A specific scoring for the ALD brain has been devised, called the Loes score. An experienced neuroradiologist can assign a Loes score of 0-34 to the MRI images; the higher the number the more severe the demyelination.

Brain MRI changes precede the clinical manifestations and aid in predicting the clinical course. In a study of 140 boys and men with cerebral ALD, the Loes score and the anatomic location of the lesion, together with the patient's age, was predictive of disease progression (Loes DJ, Fatemi A, Melhem ER et al. *Neurology*. 2003;61:369-374). According to Dr. Moser, "The MRI always becomes abnormal before the neurological or psychological findings."

ALD must be confirmed by biochemical assays that show abnormally high levels of saturated VLCFA in plasma. "A rapid and inexpensive way to rule out this disease is to send a peripheral blood sample," offered Dr. Salzman. "The next time a male patient with ADHD returns for follow-up, and his stimulant medication is not working, in addition to increasing the dose or switching medication, the clinician should consider a blood sample for ALD." Dr. Moser added that the blood test is only accurate in males and should not be used for heterozygote identification.

### Treatment of ALD

Accurate and early diagnosis of ALD is critical in giving these young patients the best possible prognosis. When performed in the critical early stages of cerebral involvement, hematopoietic stem-cell transplantation can stop or even reverse the progress of demyelination and cognitive deficits. In a study by Baumann et al (Baumann M, Korenke GC, Weddige-Diedrichs et al. *Eur J Pediatr*. 2003;162:6-14), 6 of 12 patients showed no further deterioration in neurological or neuropsychological assessment 5 years after transplantation; 6 patients who did progress had higher severity scores on MRI. In another study of 12 boys with moderate but not rapid deterioration on MRI scan, the long-term benefit of transplantation was observed 5 to 10 years later (Shapiro E, Krivit W, Lockman L et al. *The Lancet*. 2000;356:713-178). A more recent study by Peters C et al is in press in *Blood*. Drs. Moser and Aubourg both agreed that transplantation is only effective, however, in the very earliest stages of the disease, thus, early recognition is critical.

It is strongly recommended that boys younger than 15 years of age diagnosed because of a positive family history yet still symptom-free should be monitored serially for the earliest evidence of demyelination. These tests should include MRI scans (with T1, T2, and FLAIR sequences) at least every 6 months, neuropsychological measures, and endocrinologic tests to evaluate for adrenal insufficiency. A Loes score of 2-3 and/or gadolinium enhancement in a patient aged 10 or younger is highly predictive of subsequent progressive cerebral demyelination and neurological deterioration. These patients are candidates for immediate stem-cell transplantation (Peters C, Steward CG et al. *Bone Marrow Transplantation*. 2003;31:229-239). Older patients can be monitored less frequently.

Dietary therapy is of less certain benefit. The aim is to reduce the burden of VLCFA with glycerol trioleate-trierucate oil ("Lorenzo's oil"), which competes for the same enzyme system. While dietary therapy lowers VLCFA, it does not prevent neurologic deterioration in symptomatic patients. Similarly, immunotherapy may reduce the inflammatory process but has not proven to be of clinical benefit.

Adrenocortical insufficiency is treated with adrenal steroid replacement therapy. If left untreated, it can result in severe morbidity and even death. "Any child diagnosed with Addison's disease [adrenocortical insufficiency] must also be screened for ALD, as this is the most common reason for childhood Addison's," emphasized Dr. Salzman.

### Genetic Counseling and Screening

It is recommended that diagnostic tests be offered to all at-risk relatives of ALD patients, including members of the extended family. Extended-family screening, in one large study (Bezman L, Moser AB, Raymond GV et al. *Ann Neurol*. 2001;49:512-517), led to the identification of a considerable number of persons with ALD and also gene carriers. Extended-family screening can lead to the identification of asymptomatic males at a time when therapy has the greatest chance of success. Identification of heterozygotes can aid disease prevention through genetic counseling.

"Extended family screening is by far the best way to detect boys at a time when treatment can benefit them, before they are symptomatic. Unfortunately, this is not being systematically done," Dr. Moser emphasized. "The single most important thing we can do is to prevent new cases. When a child is born with ALD, his life and the life of his family will never be the same." Mass neonatal screening, while it may be desirable, is not yet technically feasible. "Prenatal screening and carrier screening, however, are currently available, and in the case of positive screens we now have reproductive technology that can facilitate family planning and allow affected persons to have unaffected offspring," said Dr. Salzman.

A minimum of 3 ml whole blood should be collected in a lavender (EDTA) tube. Results are most reliable when a fasting sample is tested. Ideally, the patient should not eat or drink 8 hours prior to blood collection. Note that drinking water is fine and will not interfere with results. The sample should be maintained at room temperature and not subjected to extremes of either heat or cold. Sample should be shipped via overnight mail, such as FedEx, and insulated as necessary (standard styrofoam blocks generally work well) The requisition form may be downloaded at <http://genetics.kennedykrieger.org/forms/pero1.pdf>. Results are available within 7 to 10 days, unless there are special circumstances.

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### Conclusion

Adrenoleukodystrophy is a devastating, often fatal condition striking young males. Early diagnosis and intervention vis-à-vis stem cell transplantation--though invasive and risky--can effectively halt the progression of the disease. Many patients die of ALD due to lack of a prompt diagnosis. **Symptoms of ALD often mimic developmental and behavioral problems of childhood, in particular, attention deficit hyperactivity disorder and visuo-motor deficits.** It behooves clinicians to learn to distinguish ALD from such conditions, and to promptly order the necessary diagnostic tests when ALD is suspected. Treatment at a very early stage of the disease is of the utmost importance in the care of these patients, and allows for timely screening of the extended family to prevent new cases and to intervene in patients before symptoms develop.

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This MediView™ Express Report discusses “Avoiding the Misdiagnosis of Adrenoleukodystrophy: Distinguishing ALD from ADD/ADHD.” Other related presentations and articles of interest include:

1. Aubourg P and Chaussain JL. Adrenoleukodystrophy: The most frequent genetic cause of Addison's Disease. *Horm Res.* 2003;59(suppl 1):104-105.
2. Baumann M, Korenke GC, Weddige-Diedrichs A et al. Haematopoietic stem cell transplantation in 12 patients with cerebral X-linked adrenoleukodystrophy. *Eur J Pediatr* 2003;162:6-14.
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. Dubois-Dalq M, Feigenbaum V, Aubourg P. The neurobiology of X-linked adrenoleukodystrophy, a demyelinating peroxisomal disorder. *Trends Neurosci.* 1999;22:4-12.
5. Ievers CE, Brown RT, McCandless SE et al. Case studies: Psychological test findings for two children with X-linked adrenoleukodystrophy. *Develop Behav Pediatr.* 1999;20(1):31-35.
6. Kemp S, Pujol A, Waterham HR et al. ABCD1 mutations and the X-linked adrenoleukodystrophy mutation database: role in diagnosis and clinical correlations. *Human Mutation.* 2001;18:499-515.
7. Loes DJ, Fatemi A, Melhem ER et al. Analysis of MRI patterns aids prediction of progression in X-linked adrenoleukodystrophy. *Neurology.* 2003;61:369-374.
8. Melhem ER, Barker PB, Raymond GV et al. X-linked adrenoleukodystrophy in children: Review of genetic, clinical, and MR imaging characteristics. *Am J Roentgenol.* 1999;173:1575-1581.
9. Moser HW, Loes DJ, Melhem ER et al. X-Linked adrenoleukodystrophy: Overview and prognosis as a function of age and brain magnetic resonance imaging abnormality. A study involving 372 patients. *Neuropediatrics.* 2000;31:227-239.
10. Peters C and Steward CG. Hematopoietic cell transplantation for inherited metabolic diseases: An overview of outcomes and practice guidelines. *Bone Marrow Transplantation.* 2003;31:229-239.

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