

Adrenoleukodystrophy Information for Physicians and Other Health Care Professionals

Definition

Adrenoleukodystrophy (ALD), an inherited condition, damages the membrane (myelin sheath) that insulates nerve cells in the nervous system. In adrenoleukodystrophy (ALD), the body cannot break down very long-chain fatty acids (VLCFAs), causing saturated VLCFAs to build up in the brain, nervous system and adrenal gland. The most common type of ALD is X-linked ALD, which is caused by a genetic defect on the X chromosome. X-linked ALD (X-ALD) affects males more severely than females, who are carriers of the disease.

Clinical Symptoms

Newborns with ALD appear healthy at birth. ALD involves multiple organs, but primarily the brain and spinal cord. Cerebral ALD is the most devastating consequence of ALD. Normal healthy males suddenly begin to regress developmentally. At first, the child will display minor behavioral problems, such as acting withdrawn, difficulty concentrating, vision problems, and coordination issues. Gradually, as the disease spreads throughout the brain, the symptoms worsen causing blindness, deafness, seizures, loss of muscle control, adrenal insufficiency, and progressive dementia. This regression leads to a vegetative state and death usually within 2-5 years of diagnosis.

Males: There are three types of X-ALD found in males. There is wide variability in the severity of X-ALD and age of onset, even among family members. Newborn screening cannot distinguish the difference between the three types. The three types (in order of severity), and symptoms if untreated, include:

- **Childhood Cerebral Demyelinating (CALD):** Learning and behavior problems (ADHD-like behavior) beginning at 4 to 10 years of age that advances to multiple neurological issues as demyelination progresses, leading to total disability and death within a few years of symptom onset.
- **Adult Onset Adrenomyeloneuropathy (AMN):** Symptoms generally begin at 20 to 30 years of age with development of progressive stiffness and weakness in legs, bladder and bowel problems, and adrenocortical insufficiency.
- **Addison's Disease Only:** Adrenal insufficiency symptoms such as unexplained vomiting, fatigue, weakness, skin darkening, and coma. Individuals are at risk for developing AMN or the cerebral demyelinating type. Addison's disease is seen in 70% of ALD cases.

Carrier Females: Female carriers can develop milder symptoms of AMN in adulthood, typically around age 40 to 50. Cerebral or adrenal disease is rare. Some female carriers never exhibit disease symptoms.

Newborn Screening and Definitive Diagnosis

In Illinois, newborn screening for adrenoleukodystrophy is performed on a dried blood spot sample using high-performance liquid chromatography (HPLC) coupled to electrospray ionization (ESI) and tandem mass spectrometry (MSMS) to detect elevated C26:0 Lysophosphatidylcholine (C26LPC) levels. **If newborn screening results indicate an elevated C26LPC level, referral should be made immediately to a pediatric metabolic disease specialist.**

Treatment

There is no cure for X-ALD currently. Early recognition of X-ALD allows the opportunity for lifesaving treatment, which can halt the disease. Asymptomatic boys with X-ALD must be closely monitored by a team of health care providers including: genetic, neurology and endocrinology specialists. Magnetic Resonance Imaging (MRI) is necessary to observe and identify changes in the brain and begin lifesaving treatment to prevent progression of the disease. Treatment will be determined in consultation with a specialist team and may include adrenal hormone replacement and hematopoietic stem cell transplant. Adrenal steroid replacement is essential for treating adrenal insufficiency, however it does not prevent the development or progression of neurological symptoms. Hematopoietic stem cell transplant is the only proven successful treatment for the cerebral form of X-ALD but must be performed in the early stages of the childhood cerebral form to be effective.

Incidence

The overall incidence of ALD is one in every 17,000 births and one in every 21,000 males. The incidence of X-ALD carrier status is one in every 14,000 female births. ALD is found in all ethnic groups.

Pathophysiology

Adrenoleukodystrophy is an X-linked peroxisomal disorder affecting the metabolism of very long chain fatty acids. ALD is caused by a mutation in the gene ABCD1, which encodes the transmembrane protein that transports VLCFAs from the cytosol into the peroxisome for catabolism. Individuals with ALD have an excess accumulation of VLCFAs in body fluids and tissues, including the white matter of the brain, Leydig cells in the testes and the adrenal cortex. This accumulation disrupts normal cell function, resulting in many health complications, including adrenal insufficiency (Addison's disease) alone, or in combination with varying neurological symptoms. Evaluation of an elevated C26LPC level found on ALD newborn screening may detect other peroxisomal disorders characterized by accumulation of VLCFAs, such as Zellweger spectrum disorder.

Inheritance Patterns

The ABCD1 gene for X-ALD is found at chromosome Xq28. It is an X-linked recessive disorder, which means that affected males cannot pass the X-ALD gene on to their sons but will pass the X-ALD gene on to their daughters. Women who have one X-ALD gene (heterozygous) have a 50% chance of passing that affected gene on to their children (male or female). Once a newborn is diagnosed with X-ALD, it is imperative that all family members are tested as asymptomatic males may be detected before symptoms occur thus allowing for the best chance for effective interventions. **Genetic counseling is recommended for families planning future pregnancies.**

Key Points for Parents

Parents should be aware not all newborns identified as having elevated C26LPC activity through newborn screening will be diagnosed with ALD. If untreated, this disorder can cause life threatening health problems. If the newborn needs additional testing or diagnostic evaluation, parents must understand the importance of following the pediatrician's and/or specialist's recommendations for additional testing and referrals. Ongoing monitoring of the child with ALD is critical.

Following Confirmation of Diagnosis

These guidelines should be followed when a diagnosis of ALD has been confirmed:

- 1) Follow up with a pediatric geneticist or metabolic specialist.
- 2) Health care providers should offer parents information on support services, such as, the local health department, the University of Illinois at Chicago Division of Specialized Care for Children (DSCC) and The Adrenoleukodystrophy Foundation.
- 3) Use of a multidisciplinary approach for long-term management including specialists from pediatrics, genetics, neurologists, endocrinologists and other disciplines as needed.
- 4) Additional information about newborn screening can be found at:
 - Baby's First Test: <http://www.babysfirsttest.org/>
Health Resource and Service Administration (HRSA), Grant no. U36MC16509, Quality Assessment of the Newborn Screening System.

- National Center for Biotechnology Information: <http://www.ncbi.nlm.nih.gov/gtr/>
National Center for Biotechnology Information, U.S. National Library of Medicine, 8600
Rockville Pike, Bethesda MD, 20894 USA.

Approved 5-29-2019