

FACT SHEET:  
X-LINKED ADRENOLEUKODYSTROPHY  
(X-ALD)

**What are the clinical symptoms of X-linked adrenoleukodystrophy?**

There are a wide range of clinical severities of X-linked adrenoleukodystrophy (X-ALD), and these have been classified into six broad categories: childhood cerebral ALD, adolescent cerebral ALD, adult cerebral, adrenomyeloneuropathy, adrenal insufficiency-only, and symptomatic heterozygotes. The clinical phenotypes of each are described below.

*Childhood cerebral ALD.* Childhood cerebral ALD is one of the most common forms of X-linked ALD, comprising approximately 30% of all patients with X-ALD. Onset of childhood cerebral ALD occurs between the ages of 2 and 10. Up to the point of onset, development is normal. The most common initial symptoms are difficulty in school, behavioral disturbance, impaired vision, or impaired hearing. After initial neurological symptoms appear, the health of the patients deteriorates rapidly. Further symptoms may include dementia, poor coordination, seizures, hyperactivity, difficulty with speech, and headaches. The average time between the initial symptoms and a vegetative state (where the patient is bedridden) or death is approximately 2 years, although it can range anywhere from 6 months to 20 years.

*Adolescent cerebral ALD.* A small number of patients with X-linked ALD will present between the ages of 11 and 21 years. The symptoms are similar to those of childhood cerebral ALD, though progression of the disease may be somewhat slower.

*Adrenomyeloneuropathy (AMN).* AMN is the most common form of the disease, and comprises approximately 40% of all X-ALD patients. The first symptoms of AMN usually occur in the twenties. Generally, initial symptoms noted are stiffness/clumsiness in the legs, weight loss, attacks of nausea, and generalized weakness. Adrenal impairment occurs, and

other major manifestations may include difficulty with walking, urinary disturbance and impotence, cognitive defects, emotional disturbances, and depression. The disease progresses slowly, and within 5 to 15 years the patient will generally need the aid of a cane or wheelchair.

*Adult cerebral ALD.* Adult cerebral ALD is relatively rare, only representing approximately 3% of all ALD cases. Age of onset varies from the 20s to the 50s. The symptoms are similar to those of schizophrenia with dementia, and the progression of the disorder is rapid. The average time from the initial symptoms to vegetative state or death is approximately 3-4 years.

*Symptomatic heterozygotes.* Women have two copies of the X chromosome, which is where the gene responsible for X-ALD resides. As a result, most women who carry a defective copy of a gene on the X-chromosome also carry one good copy of the gene, so they often won't have any symptoms of the disease. However, some women who carry one good copy and one bad copy of the X-ALD gene (heterozygotes) do show some symptoms of ALD. The symptoms can range from very mild to very severe. They resemble those of other ALD patients, with the exception that heterozygote women rarely have impaired adrenal function.

**Which of the above disorders is the most common?**

The below list is based on patients that have been seen at the hospital, so those with milder symptoms/no symptoms may be underrepresented.

- 48% - Childhood ALD
- 26% - Adrenomyeloneuropathy
- 10% - Addison Disease Only
- 8% - Presymptomatic/Asymptomatic
- 5% - Adolescent Cerebral ALD
- 3% - Adult Cerebral ALD

## How is X-ALD diagnosed?

X-ALD is diagnosed by a simple blood test that analyzes the amount of very long chain fatty acids; the levels of these molecules are elevated in X-ALD. While the test is accurate in males, in about 20% of women who are proven carriers, the test shows normal results and thus gives a "false negative" result. A DNA-based blood test is available. This test permits accurate identification of carriers by genetic testing, and if it is normal can assure a woman that she is not a carrier. Diagnostic testing, carrier screening and prenatal diagnosis are available and testing protocols are available from the United Leukodystrophy Foundation (ULF).

If the blood test suggests X-ALD, then generally an MRI will be performed in order to assess cerebral involvement. Additionally, the patient will be evaluated for adrenal insufficiency (by another blood test), as this is a common symptom of the disease that can be corrected.

## What is the cause of X-ALD?

The peroxisome is a cellular compartment that is responsible for the breakdown of certain types of fatty acids (very long chain fatty acids). Please see <http://www.peroxisome.org> for more information on the peroxisome. In X-ALD, this ability is impaired, resulting in the accumulation of very long chain fatty acids. This leads to the breakdown of the myelin sheath, resulting in the neurologic problems characteristic of leukodystrophies.

The gene that is defective in X-ALD is called ABCD1, and encodes a protein called ALDP (which stands for ALD protein). This protein resides in the wall of the peroxisome, and is involved in the breakdown of fatty acids. However, its exact role in this process is currently unclear.

It is worth noting that the specific mutation present in the ALD gene does not necessarily predict the course of the disease. Practically, this means that the fact that two members of a single family harbor the same mutation does NOT mean that the clinical course of the disease will be identical.

## How is X-ALD inherited?

There are two human sex chromosomes -- the X and the Y, and the combination of these chromosomes determines the sex of an individual. Men have one X and one Y chromosome, while women have two X

chromosomes. Likewise, men have only one copy of genes on the X chromosome, while women have two copies of these genes. If a man has a defect in a gene on an X chromosome, he may suffer from a disease because he only has the one copy of the gene; this disease is termed an X-linked disease. However, women may have a defective gene on one of the X chromosomes, but they are likely to have a normal copy of the gene on their other X chromosome. As a result, women are less likely to develop the disease.

Practically, what does this mean? It means that mostly men suffer from X-linked disorders. The disease can be passed through the women, but they may not show any symptoms of the disorder (these women are called carriers). If a carrier has daughters with an unaffected man, the daughters have a 50% chance of being carriers for the disease. These daughters may show some symptoms, but are unlikely to have the full-blown disease. If a carrier has sons with an unaffected man, the sons have a 50% chance of getting the disease.

As we mentioned before, the gene responsible for X-ALD is present on the X chromosome, which leads to the X-linked inheritance pattern seen in this disease. Please see our fact sheet on Genetic Inheritance for more information.

## Can female carriers display symptoms of X-ALD?

Women carriers of a defective ALD gene can display symptoms, though many remain asymptomatic for their entire lives. The symptoms vary dramatically, and tend to be displayed in later life. Symptoms may be similar to those of AMN (described earlier), though they are generally milder. Roughly half of all women who are carriers of X-ALD will eventually develop some sort of AMN-like symptoms in later life.

## What are the treatments for X-ALD?

1. The first treatment deals with the replacement of the faulty adrenal function often present in X-ALD. The adrenal glands are next to the kidney, and produce certain important hormones. If the adrenal functions are not properly functioning, these hormones need to be replaced. If adrenal function is reduced, provide replacement therapy.

2. Lorenzo's oil. This is a mixture of two oils (glyceryl trioleate, or GTE, and glyceryl trioleate, or GTO). It

is thought to aid in the normalization of the fatty acid levels. However, this oil does not seem to alter the progression of the disease once the brain is involved. It is not yet clear if Lorenzo's oil could prevent progression prior to symptoms.

3. Bone marrow transplantation. This is the most successful treatment for X-ALD so far identified. However, it must be noted that bone marrow transplantation has not been successful in patients with advanced neurological involvement, but only in patients in earlier stages of the disease.

### **How is research on X-ALD progressing towards better treatment and care for those with the disease?**

The identification of the gene that is mutated in X-ALD is a great step forward in the study of this disease. Gene therapy becomes a possibility, which is a method by which the defective gene is replaced by a functional copy of the gene. This type of therapy is currently being studied in animal models of X-ALD.

In addition, scientists are testing various therapeutics in animal models of X-ALD, as well as in clinical studies in patients with X-ALD. It is hoped that these studies will eventually lead to better treatments for X-ALD.

### **Are there other names for X-ALD?**

Other clinical names you might encounter for X-ALD include:

- Schilder's disease
- Sudanophilic leukodystrophy