

Newborn Screening for X-linked Adrenoleukodystrophy: Information for Parents



**Baby girl
with ABCD1
gene mutation**



**Department
of Health**

**Wadsworth
Center**

What is newborn screening?

Newborn screening involves laboratory testing on a small sample of blood collected from newborns' heels. Every state has a newborn screening program to identify infants with rare disorders, which would not usually be detected at birth. Early diagnosis and treatment of these disorders often prevents serious complications.

What is adrenoleukodystrophy (ALD)?

ALD is one of over 40 disorders included in newborn screening in New York State. It is a rare genetic disorder. People with ALD are unable to breakdown a component of food called very long chain fatty acids (VLCFA). If VLCFA are not broken down, they build up in the body and cause symptoms.

How does New York State screen for ALD?

NYS screens for ALD by measuring the amount of a specific VLCFA (C26:0) in a sample of the baby's blood. If VLCFA are elevated on the newborn screen, then genetic testing is done to look for a mutation in the *ABCD1* gene. A mutation in the *ABCD1* gene causes ALD.

My baby girl had a positive newborn screen for ALD. Does she have ALD?

No. Your daughter does not have ALD. Only boys have ALD. Because a gene mutation was found in your daughter's *ABCD1* gene, she is a *carrier* of ALD. Carriers do not develop the

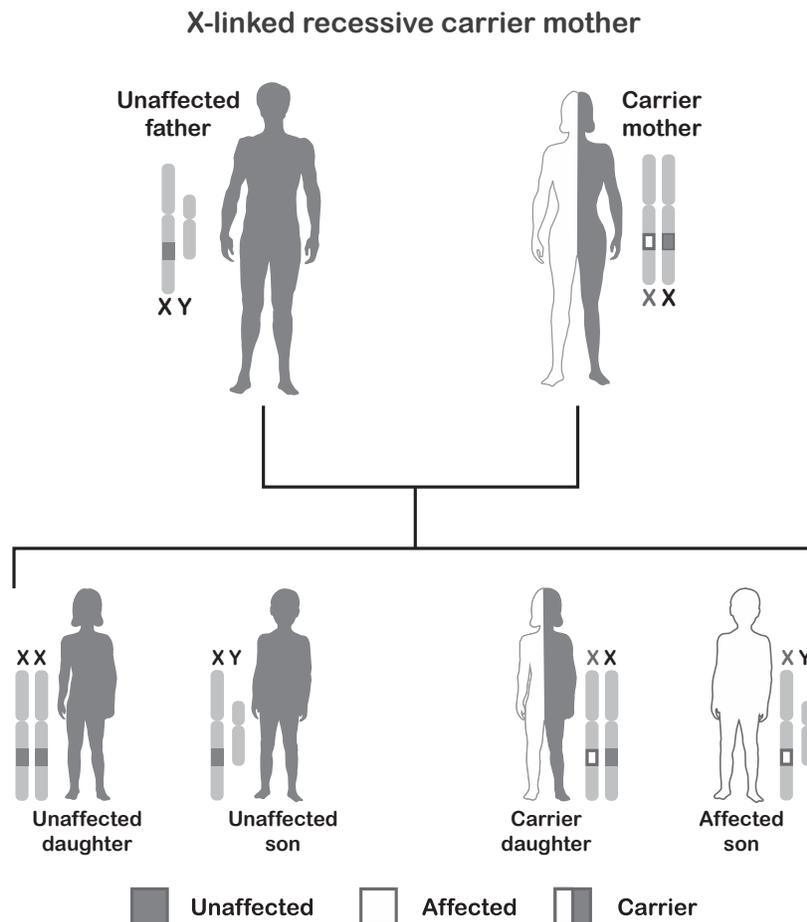
symptoms of ALD during childhood. Rarely, some women who are carriers of ALD develop mild symptoms as adults. It is important for your family to meet with a genetic counselor to talk about the genetics of ALD and implications for other family members.

Why do only boys have ALD?

Only boys have ALD because it is caused by a mutation in a gene (*ABCD1*) on the X chromosome, called "X-linked inheritance." Males only have one X chromosome so they have one *ABCD1* gene. Males with a nonfunctioning *ABCD1* gene have ALD. Females have 2 X chromosomes, so they have two *ABCD1* genes. Females with one *ABCD1* gene mutation will be carriers. When a mother is a carrier of ALD, each son has a 50% chance of inheriting the disorder and each daughter has a 50% chance of being a carrier.

Does one of the parents have an *ABCD1* gene mutation if their daughter is a carrier?

Usually an *ABCD1* gene mutation is inherited from a parent. Rarely, the mutation is not inherited and no one else in the family has it. Genetic testing for the mutation found in your daughter is available to both parents at the Newborn Screening Program. If the father has an *ABCD1* gene mutation, he could have a late onset form of ALD called AMN, but not have symptoms yet. It is very important for the parents to meet with a genetic counselor prior to the genetic testing.



What are the symptoms of ALD?

There are usually no clues at birth that a baby has ALD. X-linked ALD occurs in males. The symptoms of ALD can be different from one boy to the next. The disorder is called adrenoleukodystrophy because symptoms may involve the adrenal glands and a brain abnormality called leukodystrophy. There are three main types: childhood onset, Addison disease only and adult onset. There is no way to tell which type a boy will have until they develop symptoms.

Childhood Onset

Symptoms of the childhood onset type may include either adrenal symptoms, brain symptoms or both.

Adrenal symptoms: The adrenal glands are responsible for producing the hormones that respond to stress. A low level of these hormones can happen in boys with ALD and is also known as Addison disease. Without treatment, symptoms of Addison disease include vomiting, fatigue, low blood pressure, weakness, increased skin pigmentation and coma.

Brain symptoms: Leukodystrophy is a loss of the protective coating (“white matter”) around the nerves that make up the brain. Boys with X-linked ALD may develop leukodystrophy during childhood that causes increasing loss of developmental skills, seizures and eventually death. About 1/3 (30%) to 1/2 (50%) of boys with ALD develop leukodystrophy anytime from 3 to 21 years of age.

Adult Onset

Up to 40% of men with ALD will have the adult onset type, which may begin as early as the 20s. The adrenal symptoms are the same as the childhood type, but the neurological symptoms may be different. The neurological symptoms are called adrenomyeloneuropathy (AMN), which varies from progressive weakness of the legs and paralysis over decades to a progressive brain disease similar to the childhood onset.

Addison Disease Only

About 10% of boys with ALD will only develop adrenal symptoms anytime from age 2 to adulthood. This type is called Addison disease only because leukodystrophy never develops, but most boys with this type will develop AMN in adulthood.

Some women who are carriers of ALD develop milder neurological symptoms similar to AMN in men. The symptoms may begin around 30 years old.

What is the treatment for ALD?

Boys with ALD should regularly see doctors specializing in Neurology and Endocrinology. They will need to have a brain study called an MRI every year and blood tests to check their adrenal hormones every six months. Boys with adrenal symptoms are treated with steroid hormone replacement therapy as soon as the hormone blood tests are abnormal. As

soon as leukodystrophy can be seen on a brain study (MRI), boys are treated with a hematopoietic stem cell transplant (HSCT). Because HSCT is a very serious medical procedure, it is not done unless there are signs of leukodystrophy. A dietary supplement, Lorenzo’s oil, in conjunction with a special diet lowers very long chain fatty acids and its role as a preventative treatment is under investigation.

What caused the VLCFA to be elevated if my daughter does not have ALD?

VLCFA can be elevated in some carriers, even though they don’t have ALD. Increased VLCFA in the blood can also be caused by peroxisomal disorders other than ALD. The VLCFA are broken down in a part of the cell called the peroxisome.

What are peroxisomal disorders?

Peroxisomal disorders are rare genetic conditions. People with peroxisomal disorders are unable to breakdown a component of food called very long chain fatty acids (VLCFA). The VLCFA are broken down in a part of the cell called the peroxisome. The peroxisome’s job in the cell is to breakdown some components of food so the body can use it for energy and to make other substances needed by the body.

In Zellweger spectrum disorders (ZSD), the peroxisomes are either missing from the cell or there are too few of them. In other peroxisomal disorders, an enzyme in the peroxisome is not functioning (acyl-CoA oxidase deficiency and D-bifunctional protein deficiency).

How do I find out if my daughter has a peroxisomal disorder?

Your doctor will ask you to take your baby to see a special doctor, called a biochemical geneticist because they are experts at diagnosing peroxisomal disorders. Additional blood tests will be ordered by the specialist to find out if your baby has a peroxisomal disorder. **The additional tests are very important.**

What are the types of peroxisomal disorders?

There are different types of peroxisomal disorders. Zellweger spectrum disorder is used to describe a group of three conditions including Zellweger syndrome (ZS), neonatal adrenoleukodystrophy (NALD) and infantile refsum disease (IRD). Peroxisomal disorders also include acyl-CoA oxidase deficiency and D-bifunctional protein deficiency. Even though these disorders have different names, the symptoms are similar.

What are the symptoms of peroxisomal disorders?

Zellweger syndrome is the most severe ZSD. Children with ZS usually have symptoms at birth. Their symptoms include very low muscle tone, poor feeding, seizures, hearing loss, vision loss and liver cysts. Newborns with ZS may also have a bone abnormality in their knees and legs called chondrodysplasia punctata. Newborns with ZSD usually have a flattened appearance to their face with a broad nose. Most babies with ZS die in the first year of life.

The symptoms of NALD and IRD are similar to ZS, but less severe. Symptoms usually begin after the newborn period. The age symptoms are first noticed and the severity of symptoms is variable. Children with NALD and IRD may have a severe disorder including low muscle tone, seizures, hearing loss, vision loss and liver cysts. They may also have episodes of bleeding (hemorrhage), which can happen in the brain. Children with NALD and IRD usually have developmental delay and some will never learn to walk and talk. Some children with NALD and IRD develop a condition in their brain called leukodystrophy. In leukodystrophy, the protective coating around the nerves in the brain (myelin) is slowly lost. Children with leukodystrophy lose developmental skills and eventually it causes their death.

Rarely, some children with NALD and IRD may have milder symptoms. They learn to walk and talk later than other children (developmental delay) and may have hearing/vision problems, but otherwise are healthy.

D-bifunctional protein deficiency and acyl-CoA oxidase deficiency are both very rare disorders. The symptoms are similar to ZSDs. Most children with these disorders die in early childhood.

What is the treatment for peroxisomal disorders?

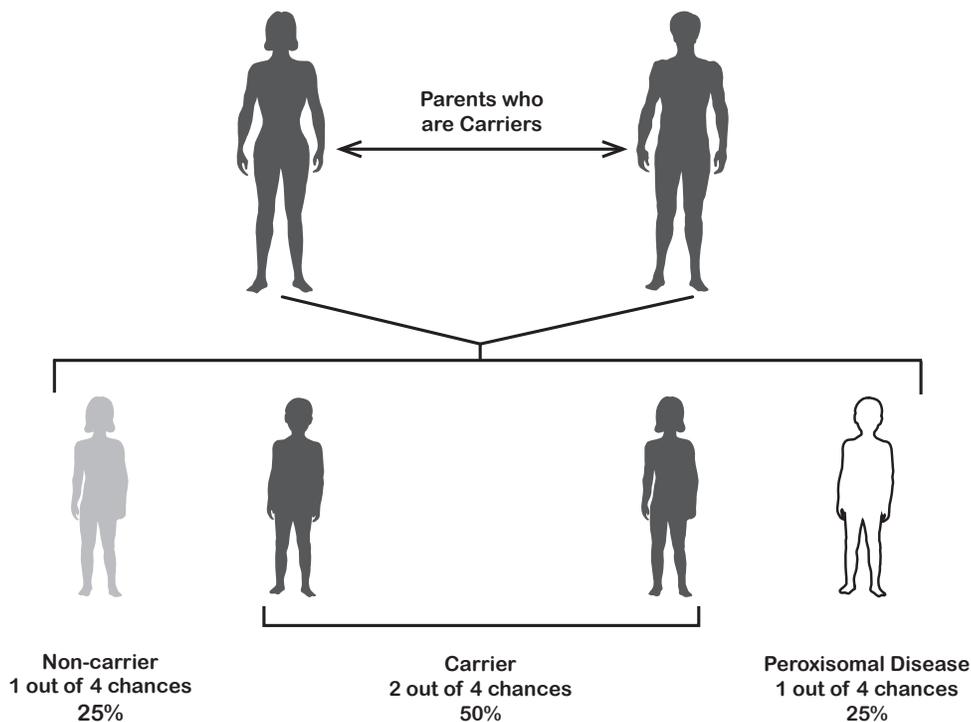
Unfortunately, there is not a treatment for peroxisomal disorders. If a peroxisomal disorder is identified early, doctors can watch for the possible symptoms and monitor nutrition, bones, liver, hearing, vision and development. Depending on symptoms, interventions may include high calorie formula, glasses, hearing aides, seizure medication, developmental therapies and vitamin K for liver disease.

What is the chance for other family members to inherit a peroxisomal disorder?

Mutations in one of several genes cause peroxisomal disorders. Each parent of a newborn with a peroxisomal disorder typically has one functional and one mutated gene and is considered a carrier. When both parents are carriers, the chance of a newborn inheriting two mutated genes is 25%.

Who can I call if I have additional questions about newborn screening for ALD?

Your baby's doctor and the NYS Newborn Screening Program are resources for additional questions about newborn screening for ALD.



Wadsworth Center's Newborn Screening Program

P.O. Box 509
Albany, NY 12201-0509

518-473-7552

www.wadsworth.org/newborn/index.htm