Kansas Department of Health and Environment

Newborn Screening
Info Sheet

KANSAS NEWBORN SCREENING PROGRAM

X-Linked Adrenoleukodystrophy (X-ALD)

X-linked adrenoleukodystrophy (X-ALD) is an inherited (genetic) condition that prevents the body from breaking down certain fats that are important in certain parts of the body like the brain, spinal cord, as well as the adrenal glands, which help produce certain hormones in the body.

Clinical Symptoms

In X-ALD, the protein ALDP is not made correctly, so these fats cannot enter peroxisomes to be processed. These VLCFA build up over time and damage the nervous system (including the brain and spinal cord) and the adrenal glands, which produce important hormones.

Damage caused by the buildup of VLCFA in the adrenal glands can prevent the adrenals from producing necessary hormones. This can make it harder to recover from infections or other stress. This damage, called adrenal insufficiency, is not ordinarily seen in babies but may develop as they get older. Adrenal insufficiency can be found with a blood test.

The VLCFA can also build up in the brain. About 35 percent of boys with this buildup develop the brain, or cerebral, form of X-ALD, which is the most severe. This condition usually occurs in boys 4 to 10 years old but can be earlier or later in life. There is also an adult form of the condition that affects the spinal cord, called adrenomyeloneuropathy (AMN). AMN is generally seen in young adults.

Signs and symptoms of X-ALD typically do not appear until childhood (as early as 2 years old, but more commonly between 4 and 10 years old).

- Difficulty swallowing
- Vision problems; crossed eyes
- Hearing loss
- Difficulty reading, writing, understanding speech, and comprehending written and spoken material
- Aggressive behavior
- Hyperactivity
- Poor coordination
- Changes in muscle tone; spasms and spasticity
- Seizures
- Worsening nervous system deterioration

- Decreased fine motor control
- Paralysis
- Coma
- Adrenocortical insufficiency or Addison's disease; adrenal glands do not produce enough steroid hormones

    Adrenomyeloneuropathy (AMN):

    - Urinary and genital tract disorders
    - Progressive stiffness and weakness in the legs (paraparesis)

    Addison disease:

    - Decreased appetite
    - Darker areas of skin color or pigment
    - Vomiting
    - Loss of weight and muscle mass
    - Muscle weakness
    - Low blood sugar

Incidence

Adrenoleukodystrophy (ALD) affects 1 in 15,000 individuals (males and females) worldwide, regardless of race, ethnicity and geography. ALD affects males more severely and is more common in males because it is an X-linked condition. However, 20-40% of women who are carriers have symptoms in adulthood.

Genetics and Inheritance

Adrenoleukodystrophy is caused by mutations or changes in the ABCD1 gene. This gene provides instructions for making the protein, adrenoleukodystrophy (ALDP), which transports VLCFAs into peroxisomes. Peroxisomes are small sacs inside cells that breakdown VLCFAs and other molecules.

When the ABCD1 gene has a mutation or change, there is not enough ALDP being made, so VLCFAs are not transported and broken down correctly. This causes a build up of VLCFAs in the body, which damages the myelin and the adrenal glands leading to the symptoms seen in X-ALD.

- X-ALD is inherited in an X-linked recessive pattern, which means babies inherit this condition on their X chromosome.
    - Baby girls have two X chromosomes. Only girls with two nonworking *ABCD1* genes (one on each chromosome) have X-ALD. This is a very rare situation.
    - Baby boys only have one X chromosome. All boys with one nonworking *ABCD1* gene (on their only X chromosome) have X-ALD. This condition is more common in boys.
- Girls with one working copy and one nonworking copy of the *ABCD1* gene are called carriers.

    - Carriers for X-ALD may also have symptoms of the condition, but not generally until adulthood. Carriers for X-ALD may also have symptoms of the condition, but not generally until adulthood. Some carriers may show no symptoms, others may have mild symptoms, and others may have more significant symptoms in adulthood.
    - Carriers may pass down a nonworking copy of the gene to their children.
- Parents who already have a boy with X-ALD still have a 1 in 2 chance of another son being born with X-ALD. Parents who have a girl who is an X-ALD carrier still have a 1 in 2 chance of having another girl that is an X-ALD carrier.
    - All forms of X-ALD may be seen in the same family (cerebral form of X-ALD, adrenal insufficiency, AMN). Right now, we cannot tell who could have what type.

Treatment

Children who receive early and ongoing treatment for X-ALD can have better health outcomes than those who do not. Early stem cell transplantation can help prevent problems in children with nervous system symptoms. Treatment works best if it is given when changes are just beginning in the brain, before it becomes extensive and nervous system signs or symptoms start.

Steroids

Individuals who have adrenal insufficiency need to have regular adrenal gland testing, and can be treated effectively with replacement corticosteroids. The medication replaces what the body would have made daily but needs to be carefully monitored and adjusted as individuals grow. Illnesses and other stressors such as surgery require increased doses.

Allogeneic hematopoietic cell transplantation (HCT) or Stem Cell Transplantation

HCT is a treatment that may halt the progression of cALD in children if the disease is diagnosed and treated early. Stem cells are taken from umbilical cord blood or bone marrow from a healthy, matched donor and given to the child with cALD. These new stem cells produce the protein ALDP (explained below) that the child with cALD cannot produce himself. HCT however is a complicated procedure and not without risks.

Other Treatments

Other treatments include medication to help relieve symptoms like stiffness and seizures, and physical therapy, which can help relieve muscle spasms and reduce muscle rigidity. There is currently a clinical trial for gene therapy which may be another method to stop the progression of X-ALD.

Screening Methodology

The testing methodology X-ALD in Kansas is Liquid Chromotography-Mass Spectrometry/Mass Spectrometry Negative Ion Mode. X-ALD is caused by pathogenic variants in the ATP-binding cassette subfamily D member 1 gene (*ABCD1*) that encodes the adrenoleukodystrophy protein (ALDP). Defects in ALDP result in elevated cerotic acid, and lead to C26:0-lysophosphatidylcholine (C26:0-LPC) accumulation, which is the primary biomarker used in newborn screening (NBS) for X-ALD.

C26:0-LPC levels were measured in dried blood spot (DBS) NBS specimens using a flow injection analysis (FIA) coupled with electrospray ionization (ESI) tandem mass spectrometry (MS/MS) performed in negative ion mode.

If the C26:0-LPC levels are elevated, the newborn is referred for further diagnostic testing and genetic counseling. In newborn screening, if the baby has high levels of specific LPCs it could mean that the baby is at risk for X-ALD or another disorder such as Zellweger Syndrome.

https://pmc.ncbi.nlm.nih.gov/articles/PMC9036197/

https://www.sciencedirect.com/science/article/abs/pii/S0009898118303437#:~:text=Of%20these%2C%2014%20(43.7%)%20were%20identified%20ABCD1,males%2C%20heterozygous%20females%20and%20other%20peroxisomal%20disorders.

What to do after Presumptive Positive

1) The clinician should immediately check on the clinical status of the baby.

2) Consultation with a metabolic specialist is essential.

3) The specialist may request blood tests and MRI for baby.

4) Call KS Newborn Screening Program at 785-291-3363 with questions about results.

5) Report clinical findings to the Newborn Screening Program at 785-291-3363.

6) Same birth siblings (twins, triplets) of infants diagnosed with X- ALD should be re-screened; additional testing of these siblings also may be indicated.

7) Consider testing older siblings. Some individuals may be affected, but show no symptoms of the condition.

8) If a Kansas baby screens positive for C26:0 and the diagnosis is negative for X-ALD, the family should be referred for Zellweger Syndrome testing. Especially since the testing is offered to families at no charge. X-ALD has an extremely low false positive rate. We have Kansas listed as screening for Zellweger Syndrome in the NewSTEPS database since the XALD subcommittee recommended we refer babies for Zellweger testing if the X-ALD diagnosis was negative.

https://www.preventiongenetics.com/sponsoredTesting/Mirum_zsd

Confirmation of Diagnosis

Blood Testing:

The blood test analyzes the amount of very long chain fatty acids, which are elevated in X-ALD. This test has the highest degree of accuracy in males; however, it can sometimes miss the presence of the mutated gene in women who are carriers of the disease.

MRI:

If the blood test suggests X-ALD, a magnetic resonance imaging scan (MRI) will be performed to determine if the disease has begun to do damage to the brain. Lesions on the brain caused by the destruction of the myelin will appear on MRI before any neurological or psychological symptoms appear. The MRI scan will produce something called a Loes score, which rates the severity of the damage to the brain on a scale from 0 to 34. A score of 0.5 or less is normal; a score of 14 or more indicates severe X- ALD.

Genetic Testing:

Sequencing of the *ABCD1* gene is available to confirm the diagnosis of X-ALD, improve carrier detection, and assist with prenatal diagnosis.

Sources

https://neurology.testcatalog.org/show/XALDZ#:~:text=POX%20/%20Fatty%20Acid%20Profile%2C%20Peroxisomal,and%20assist%20with%20prenatal%20diagnosis.

https://www.stopald.org/diagnosis#:~:text=Diagnostic%20Testing.or%20more%20indicates%20severe%20ALD.

Communication of Results to Parents

If a baby is diagnosed with X-ALD, the following points should be conveyed to parents:

• Parents should understand that treatment for X-ALD will be lifelong.

• Parents should understand that treatment is not curative, and that all morbidity cannot necessarily be prevented. Long-term management, monitoring, and compliance with treatment recommendations are essential to the child's well-being. A multidisciplinary approach is recommended and includes pediatrics and a metabolic specialist. Other providers may include cardiology, physical therapy, and nutritionist.

• Genetic counseling may be indicated. A list of counselors and geneticists, whose services are available in Kansas, should be given to the parents if they have not already seen a geneticist.

Sources

https://pmc.ncbi.nlm.nih.gov/articles/PMC10296388/#:~:text=Laboratory%20Tests.mutation%20in%20the%20IDS%20gene.

Baby's First Test

HRSA Newborn Screening

Specialists:

Carolina Beltran, MD	Wesley Medical Center	Wichita, KS	Clinic Phone: 316-962-2153 Fax: 316-665-6719
Bryce Heese, MD Jennifer Gannon, MD Angela Lee, MD	Children's Mercy	Kansas City, MO	Clinic Phone: 816-234-3771 Hospital Operator: 816-234-3000 Office Fax:816-302-9963