TEXAS Health and Human Services | Texas Department of State Health Services

Newborn Screening ACT Sheet

Elevated C26:0 Lysophosphatidylcholine
X-linked Adrenoleukodystrophy (X-ALD)

Differential Diagnosis: X-linked adrenoleukodystrophy (X-ALD), other peroxisomal disorders (including Zellweger spectrum disorders).
Condition Description: X-ALD is an X-linked genetic disorder caused by a defect in the adrenoleukodystrophy protein (ALDP) causing the accumulation of abnormally high levels of very long chain fatty acids in the body. This affects the nervous system white matter and the adrenal cortex. There are 3 variants of X-ALD: a childhood cerebral form that occurs primarily in males, adrenomyeloneuropathy (AMN), and Addison-only disease. Female carriers can develop AMN but typically onset is later and milder than in affected males.

You Should Take the Following IMMEDIATE Actions

- Contact family to inform them of the newborn screening result and ascertain clinical status. No clinical signs are expected in newborns with confirmed X-ALD. The presence of symptoms (poor feeding, bony abnormalities, abnormal liver function testing, hypotonia, renal cysts) in a newborn may be suggestive of another peroxisomal disorder.
- Consult with a pediatric metabolic specialist or pediatric neurogeneticist.
- Evaluate the newborn. If any sign (above) is present or infant is ill, transport to hospital for further evaluation and treatment in consultation with metabolic/neurogenetic specialist.
- Initial labs: Collect very long chain fatty acids, and other testing as recommended by specialist.
- Provide family with basic information about X-ALD disease, and signs and symptoms.
- Repeat newborn screen if second screen has not been done.
- Report findings to newborn screening program.

Diagnostic Evaluation: Confirmatory very long chain fatty acid analysis. Patients with elevated values indicative of X-ALD or a peroxisomal disorder should have follow-up molecular genetic testing. Female carriers may also be identified.

Clinical Considerations: The childhood cerebral form of X-ALD manifests in males most commonly at around 4 to 10 years of age with attention deficit hyperactivity disorder, progressive cognitive and behavioral changes, adrenal impairment, and characteristic MRI abnormalities. X-ALD is caused by mutations in the ABCD1 gene and has an estimated incidence of approximately 1 in 17,000 live births. Adrenal steroid replacement is essential for treating adrenal insufficiency, however it doesn't prevent the development or the progression of neurological symptoms. Hematopoietic stem cell transplantation 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.

Additional Information:

Genetics Home Reference
https://ghr.nlm.nih.gov/condition/x-linked-adrenoleukodystrophy
Genetic Testing Registry
https://www.ncbi.nlm.nih.gov/gtr/conditions/C0162309/
Baby's First Test
http://www.babysfirsttest.org/newborn-screening/conditions/adrenoleukodystrophy

TEXAS Health and Human Services | Texas Department of State Health Services

Newborn Screening FACT Sheet

X-linked Adrenoleukodystrophy (X-ALD)

What is Adrenoleukodystrophy (X-ALD)?
Adrenoleukodystrophy occurs when the body's cells cannot break down very long-chain fatty acids (VLCFAs). These build up and cause problems in the brain, spinal cord and adrenal glands.

If a baby's screening result for ALD is out of the normal range, the baby's doctor will recommend additional testing. **It is important to remember that an out-of-range screening result does not necessarily mean that a baby has the condition.** But follow-up with a medical specialist is very important.

What Causes X-ALD?
X-ALD is caused by changes (usually referred to as variants) in the ABCD1 gene. This gene provides instructions for making the adrenoleukodystrophy protein (ALDP). The ALDP binds to VLCFAs and carries them to the area of the cell where they get broken down.

When the ABCD1 gene has a pathogenic variant, the ALDP is either abnormal or missing. The VLCFAs build up in the cell, causing damage to the brain, spine and adrenal glands.

The ABCD1 gene is located on the X chromosome. Females have two X chromosomes in each cell. Males have one X chromosome and one Y chromosome. One variant copy of the ABCD1 gene is enough to cause X-ALD in boys.

Females with one non-working copy of the gene and one working copy are referred to as carriers, but may also develop symptoms of X-ALD as adults.

There are three types of X-ALD: Childhood Cerebral, adrenomyeloneuropathy (AMN), and Addison's disease. Newborn screening tests are not able to identify which of the three types a baby will have.

What Symptoms Occur with X-ALD?
There are usually no symptoms of X-ALD at birth. Symptoms of X-ALD can be different depending upon the type of X-ALD, and the age and sex of the person. Common symptoms for the different types of X-ALD include:

Childhood Cerebral
This most severe type of X-ALD occurs in male patients, starting with mild symptoms that may look like Attention Deficit Hyperactivity Disorder (ADHD). Over weeks or months, symptoms become more severe and may include behavior and learning disabilities, seizures, weakness, vision loss, and hearing loss. If untreated, this form is fatal.

Adrenomyeloneuropathy (AMN)
Symptoms of AMN will not usually begin until adulthood. Patients develop leg weakness that may worsen with time, and may experience problems with the bladder and/or the genital tract. About 20 percent of individuals with AMN will develop cerebral symptoms.

Addison's disease (Adrenal Insufficiency)
If untreated, males with Addison's disease will develop adrenal symptoms including vomiting, fatigue, low blood pressure, weakness, skin darkening, and coma. These symptoms can develop as early as the first year of life and must be treated immediately.

Asymptomatic X-ALD
For some boys, it may take many years for symptoms to appear. Even if a baby/child does not have symptoms of ALD, it is important for him to be regularly checked by a neurologist and an endocrinologist.

Female Carriers
More than 50 percent of women who are carriers show some symptoms of X-ALD. These often appear later in life than in men and are usually milder, but may be severe. Some women may never show any symptoms. Adrenal insufficiency is not typically seen in women. Not all female carriers have abnormal levels of VLCFA's.

What is the Treatment for X-ALD?
X-ALD can be treated. Possible treatments include:

Stem cell transplant
This treatment may halt the progression of Childhood Cerebral X-ALD if diagnosed and treated early.

Steroids
Individuals who have adrenal insufficiency can be treated effectively with replacement corticosteroids.

Other treatments
Other treatments may include medication to relieve symptoms like stiffness and seizures; physical therapy, which can help relieve muscle spasms and reduce muscle rigidity, and experimental dietary therapies.

Gene therapy
Clinical trials using gene therapy on boys with Childhood Cerebral X-ALD are promising and may be another method to stop disease progression.