CONDITION

Alcoholic liver disease

Learn about X-linked adrenoleukodystrophy (ALD), including its neurological and adrenal symptoms, inheritance, testing, treatment options, and follow-up care.

WHAT IT IS
Rare X-linked inherited disorder affecting nerves and adrenal glands

BODY SYSTEM
Nervous system and hormone system

MAIN SYMPTOMS
Cognitive or behavioral decline, leg stiffness or weakness, difficulty walking, tiredness and weight loss

WHAT CAUSES IT
Inherited ABCD1 gene change

HOW IT IS DIAGNOSED
ABCD1 genetic testing

MAIN TREATMENT
Stem cell or gene therapy, hormone replacement, supportive care

CAN IT BE CURED?
No, treatments manage or slow damage

IS IT AN EMERGENCY?
Sometimes, severe vomiting, confusion or fainting

LONG-TERM OUTLOOK
Variable, with progressive severe disability possible

Overview

ALD usually refers to X-linked adrenoleukodystrophy , a rare inherited condition that can affect the brain, spinal cord, peripheral nerves, and adrenal glands. It is different from alcohol-associated liver disease, which is also sometimes shortened to ALD.

X-linked adrenoleukodystrophy is caused by a change in the ABCD1 gene. This gene helps the body break down very long-chain fatty acids. When the gene does not work properly, these fatty acids build up in certain tissues.

The buildup can damage myelin , the protective covering around nerve fibers. It can also damage the adrenal glands, which make hormones needed for blood pressure, energy, and the response to illness or stress.

ALD does not affect everyone in the same way. Even relatives with the same gene change may develop different symptoms at different ages. The main patterns include:

Early recognition matters because treatment for cerebral ALD is most effective before major neurological disability develops. Adrenal insufficiency can also be treated, but it may become dangerous if it is not recognized.

- Cerebral ALD , in which inflammatory damage develops in the brain
- Adrenomyeloneuropathy , or AMN, which mainly affects the spinal cord and nerves
- Adrenal insufficiency , meaning the adrenal glands do not make enough essential hormones
- An asymptomatic form, in which testing shows the gene change but symptoms have not developed

Symptoms

Symptoms depend on which parts of the body are affected. A person may have adrenal symptoms, neurological symptoms, or both.

Cerebral ALD most often begins in childhood, particularly in boys, but it can also appear during adolescence or adulthood. Early changes may be subtle and can be mistaken for learning, attention, or behavioral problems. Symptoms may include:

These symptoms may worsen over time if inflammatory brain disease remains active.

AMN usually develops in adulthood. It causes slow damage to the long nerve pathways in the spinal cord. Common symptoms include stiffness or weakness in the legs, difficulty walking, reduced balance, numbness, pain, and bladder or bowel problems. Sexual dysfunction may also occur.

People with two X chromosomes who have an ABCD1 gene change often do not develop childhood cerebral disease. However, many develop AMN-like symptoms later in adulthood, especially stiffness, weakness, pain, or bladder problems. Adrenal insufficiency and cerebral disease are less common in this group.

Adrenal insufficiency may occur before neurological symptoms. Possible signs include ongoing tiredness, muscle weakness, reduced appetite, weight loss, nausea, abdominal discomfort, dizziness when standing, low blood pressure, and unusually darkened skin. Blood tests may show low sodium or high potassium.

Severe vomiting, marked weakness, dehydration, confusion, fainting, or inability to keep down prescribed steroid medicine may indicate an adrenal crisis . This is a medical emergency and

requires immediate care.

- A decline in school or work performance
- Difficulty paying attention or processing information
- Changes in behavior or personality
- Problems with vision, hearing, speech, or swallowing
- Poor balance, clumsiness, or muscle weakness
- Seizures
- Loss of previously learned abilities

Causes and risk factors

ALD results from a disease-causing change in the ABCD1 gene on the X chromosome. The gene makes a protein that transports very long-chain fatty acids into structures called peroxisomes, where the fats are broken down. A faulty protein allows these fats to accumulate.

Because the condition is X-linked, it often affects people with one X chromosome more severely. A person with two X chromosomes may have one working copy of the gene that provides partial protection, although neurological symptoms can still develop later in life.

A parent can pass the gene change to a child. A parent with two X chromosomes and one altered ABCD1 copy has a 50% chance of passing that altered copy in each pregnancy. A father with the gene change passes it to all of his daughters and none of his sons.

The specific gene change does not reliably predict when symptoms will begin or how severe they will become. Family members with the same variant may have very different experiences. Environmental or other genetic factors may influence the course, but these are not fully understood.

Having an ABCD1 variant creates the risk for ALD. It does not mean that cerebral disease is certain to develop. There is no evidence that ordinary activities, diet, or parenting choices cause the condition.

Diagnosis

ALD may be identified through newborn screening, evaluation of symptoms, or testing after a relative is diagnosed. Newborn screening programs in many parts of the United States test for

a fatty acid marker associated with ALD. A positive screen does not confirm the diagnosis; additional testing is required.

Blood tests can measure very long-chain fatty acids or a related marker called C26:0-lysophosphatidylcholine. Results are usually clearly abnormal in affected males. Standard fatty acid testing can be normal in some females with an ABCD1 variant, so genetic testing is important when ALD is suspected.

Genetic testing can identify a disease-causing ABCD1 variant and confirm the diagnosis. A genetics professional can explain what the result means for the individual and their relatives.

Other testing may include:

MRI findings help distinguish cerebral ALD from spinal cord disease. Because early cerebral changes may not cause noticeable symptoms, scheduled MRI surveillance is important for boys and men with an ABCD1 variant, even when they feel well.

Testing may also be offered to close biological relatives. This is sometimes called cascade testing. It can identify family members who need neurological or adrenal monitoring.

- Brain magnetic resonance imaging, or MRI, to look for changes in the brain's white matter
- MRI with contrast to determine whether a brain lesion shows active inflammation
- Morning cortisol and adrenocorticotropic hormone, or ACTH, tests to evaluate adrenal function
- Neurological examination and assessments of walking, strength, sensation, vision, hearing, or thinking
- Additional hormone and electrolyte tests when adrenal insufficiency is suspected

Treatment and management

Treatment depends on the form of ALD, the person's age, symptoms, MRI findings, and overall health. Care often involves specialists in neurology, endocrinology, genetics, rehabilitation, and stem cell transplantation.

For early cerebral ALD, allogeneic hematopoietic stem cell transplantation may stop or slow inflammatory brain damage. The procedure replaces blood-forming stem cells with cells from a suitable donor. It has the greatest chance of preserving function when treatment occurs early, before extensive symptoms or MRI changes develop.

A transplant cannot reliably restore abilities that have already been lost. It also carries serious risks, including infection, organ injury, graft-versus-host disease, infertility, and treatment-related death. A specialized transplant team evaluates the expected benefits and

risks for each patient.

Elivaldogene autotemcel, sold as Skysona, is a gene therapy approved in the United States for certain boys with early, active cerebral ALD. It uses the patient's own blood-forming stem cells, modified to carry a working copy of the relevant gene. It is not suitable for every patient.

Skysona has a boxed warning for blood cancers, including myelodysplastic syndrome and leukemia. People who receive it require long-term blood testing and monitoring. Treatment decisions should be made at an experienced center after discussion of gene therapy, donor transplantation, and the risks of untreated cerebral disease.

Adrenal insufficiency is treated with hormone replacement, usually a glucocorticoid that replaces cortisol. Some people also need a mineralocorticoid to support salt balance and blood pressure. The prescribing clinician provides instructions for increasing glucocorticoid treatment during fever, surgery, injury, or other physical stress. Patients may be advised to carry emergency medication and medical identification.

Hormone replacement treats adrenal insufficiency but does not treat neurological damage.

There is no established treatment that reverses spinal cord damage from AMN. Management focuses on function and comfort. It may include physical and occupational therapy, stretching, mobility aids, treatment for muscle stiffness or nerve pain, and care for bladder, bowel, or sexual symptoms.

Lorenzo's oil is a specially formulated mixture of fats that can lower very long-chain fatty acid levels. It has not been shown to reverse established neurological disease. Its possible role in people without symptoms remains uncertain, and it should be discussed with a metabolic specialist rather than started without medical supervision.

Complications

Cerebral ALD can cause progressive loss of movement, communication, vision, hearing, swallowing, and thinking abilities. Advanced disease may lead to complete dependence on others for care.

AMN can gradually limit walking and daily activities. Falls, painful muscle spasms, bladder infections, constipation, and reduced independence may occur. Symptoms often progress slowly, but the course varies.

Swallowing difficulty can increase the risk of poor nutrition or food and liquid entering the lungs. Reduced mobility may contribute to pressure injuries, blood clots, and loss of muscle strength.

Untreated adrenal insufficiency may lead to adrenal crisis, especially during an infection, injury, surgery, or severe vomiting. Warning signs include severe weakness, repeated vomiting, dehydration, confusion, fainting, or very low blood pressure. Emergency medical care is needed.

Stem cell transplantation and gene therapy have their own possible complications. These include serious infection, organ damage, immune complications, infertility, and, with gene therapy, blood cancer. Treatment centers provide both short-term and long-term safety monitoring.

Follow up

ALD requires lifelong follow-up, including for people who do not currently have symptoms. The monitoring plan depends on age, sex, symptoms, previous treatment, and the form of the condition.

Children at risk for cerebral ALD generally have scheduled brain MRIs so that treatment can be considered before significant disability develops. MRI timing should be directed by clinicians experienced in ALD.

Adrenal function also needs regular assessment. New tiredness, weight loss, darkening of the skin, nausea, dizziness, or reduced ability to handle illness should be reported promptly rather than saved for a routine visit.

Adults should discuss new walking difficulty, stiffness, falls, numbness, pain, or bladder and bowel changes at follow-up appointments. Rehabilitation review can help maintain safety and independence.

Seek prompt medical assessment for new neurological symptoms, such as worsening balance, weakness, vision changes, confusion, seizures, or a noticeable decline in school or work skills. Call emergency services for a seizure lasting several minutes, loss of consciousness, severe breathing or swallowing difficulty, or possible adrenal crisis.

Genetic counseling can help with family testing and reproductive planning. Emotional support is also important because ongoing surveillance and uncertainty can be stressful for patients and families.

Sources



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