CONDITION

Adrenoleukodystrophy

Learn how adrenoleukodystrophy affects the brain, spinal cord, and adrenal glands, including symptoms, testing, treatment options, and lifelong follow-up.

WHAT IT IS
Inherited disorder affecting myelin and adrenal glands

BODY SYSTEM
Nervous and hormone systems

MAIN SYMPTOMS
Learning or behavior changes, walking difficulty, leg stiffness or weakness, fatigue

WHAT CAUSES IT
Inherited ABCD1 gene change

HOW IT IS DIAGNOSED
VLCFA blood testing and ABCD1 genetic testing

MAIN TREATMENT
Hormone replacement, stem cell or gene therapy, rehabilitation

CAN IT BE CURED?
No, lifelong follow-up remains necessary

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

LONG-TERM OUTLOOK
Variable, from asymptomatic to profound disability

Overview

Adrenoleukodystrophy, or ALD, is an inherited condition that can affect the brain, spinal cord, nerves, and adrenal glands. It is caused by changes in the `ABCD1` gene. This gene helps the body process very-long-chain fatty acids, often shortened to VLCFAs. In ALD, these fats build up in certain tissues.

ALD is usually inherited in an X-linked pattern. The `ABCD1` gene is on the X chromosome. Because males generally have one X chromosome, a disease-causing change in their single copy can lead to serious symptoms. Females generally have two X chromosomes, so the effects are often later and mainly involve the spinal cord. However, females can develop significant disability and should not be viewed only as unaffected "carriers."

ALD does not follow one predictable course. Even relatives with the same genetic change can

develop different symptoms at different ages. The main clinical patterns include:

Cerebral ALD can progress rapidly once active brain inflammation begins. Early detection matters because treatments intended to slow cerebral disease work best before major neurologic disability develops. Newborn screening in many parts of the United States now identifies some affected infants before symptoms appear.

- Cerebral ALD , which causes inflammation and loss of myelin in the brain. Myelin is the protective covering around nerve fibers.
- Adrenomyeloneuropathy , or AMN, which mainly affects the spinal cord and nerves controlling the legs, bladder, bowel, and sexual function.
- Adrenal insufficiency , in which the adrenal glands do not make enough essential hormones.
- An asymptomatic stage , when testing shows ALD but the person has no noticeable symptoms.

Symptoms

Symptoms depend on which parts of the body are affected. A person may have one form of ALD at first and develop other features later.

Cerebral ALD is most often recognized in boys, although it can occur at other ages. Early changes may be mistaken for attention, learning, behavioral, hearing, or vision problems. Possible symptoms include:

AMN usually develops in adulthood and progresses more slowly. Common symptoms include leg stiffness, weakness, poor balance, numbness, pain, and difficulty walking. Bladder urgency, urinary leakage, constipation, and sexual dysfunction may occur. Symptoms can become significant over years or decades.

Many females with an `ABCD1` change eventually develop AMN-like symptoms, particularly leg stiffness, balance problems, pain, or bladder and bowel difficulties. Cerebral disease and adrenal insufficiency are uncommon in females, but new neurologic symptoms still need medical assessment.

Adrenal insufficiency may occur before neurologic symptoms. Possible signs include ongoing fatigue, weakness, poor appetite, weight loss, nausea, vomiting, abdominal pain, low blood pressure, dizziness, and unusually darkened skin. Salt craving can occur when the body is also low in aldosterone, a hormone that helps control salt and blood pressure.

Severe vomiting, marked weakness, confusion, fainting, or inability to take prescribed steroid

medicine may signal an adrenal crisis . This is an emergency, particularly during an illness, injury, or surgery. Follow the person's emergency steroid plan and seek emergency medical care.

A first seizure, sudden loss of consciousness, severe breathing or swallowing difficulty, or a rapid neurologic decline also requires emergency evaluation.

- Declining school performance or loss of previously learned skills
- Changes in attention, behavior, coordination, or handwriting
- Difficulty understanding speech, even when hearing tests seem normal
- Vision changes
- Problems walking or using the hands
- Weakness, stiffness, swallowing problems, or seizures as disease advances

Causes and risk factors

ALD results from a disease-causing change in the `ABCD1` gene. The change prevents a cell structure called the peroxisome from transporting and breaking down VLCFAs normally. The resulting buildup is associated with injury to myelin and the adrenal cortex, the hormone-producing outer layer of the adrenal glands.

The condition is not caused by a person's diet, parenting, activity level, or anything done during pregnancy. Dietary intake contributes only a small part of the body's VLCFAs because the body also makes these fats.

A male with ALD passes his altered X chromosome to all of his daughters and none of his sons. A female with one altered copy has a 50% chance of passing that copy in each pregnancy. The child's sex does not change the chance of inheriting the copy, although it often affects how the condition appears.

Having an `ABCD1` change does not predict the exact age of onset, symptoms, or speed of progression. Genetic test results generally cannot determine whether or when a male will develop cerebral disease. For this reason, ongoing screening remains important even when someone feels well.

Sometimes ALD is found without a known family history. The genetic change may have been passed through relatives who had mild, late, or unrecognized symptoms. In other cases, it may be a new change in the affected person.

Diagnosis

ALD may be identified through newborn screening, an evaluation of symptoms, or family testing. Newborn screening measures a fat-related marker called C26:0-lysophosphatidylcholine. A positive screen does not by itself establish the diagnosis. Follow-up testing is needed promptly.

Diagnostic evaluation may include:

MRI uses a magnetic field to create detailed pictures of the brain. Contrast material may be given through a vein to look for active inflammation. Specialists can score MRI changes to help assess the extent of cerebral disease and whether a person may be eligible for treatment.

VLCFA blood testing is highly informative in males. Results can be less clear in females, so genetic testing is particularly important when evaluating a female relative.

Once an `ABCD1` change is identified, genetic counseling can help the family understand inheritance and testing options. Testing close biological relatives may identify people who need brain MRI or adrenal monitoring before symptoms begin.

ALD can overlap with other neurologic or adrenal conditions. Clinicians interpret laboratory, genetic, imaging, and clinical findings together rather than relying on any single symptom.

- Blood testing for VLCFAs or related lipid markers
- Genetic testing for a disease-causing `ABCD1` change
- Brain magnetic resonance imaging, or MRI
- Blood tests of adrenal function, including cortisol and adrenocorticotropic hormone
- A neurologic examination and assessment of walking, strength, sensation, vision, hearing, learning, or behavior

Treatment and management

Management depends on age, symptoms, adrenal function, MRI findings, and the rate of change. Care often involves neurologists, endocrinologists, transplant or gene-therapy specialists, rehabilitation clinicians, genetic counselors, and primary care professionals.

People with adrenal insufficiency need replacement of missing adrenal hormones. Glucocorticoids replace cortisol. Some people also need a mineralocorticoid to replace aldosterone. Treatment plans usually include instructions for increasing glucocorticoids during fever, injury, surgery, or other physical stress. Patients and caregivers may also be taught how to give an emergency injection when oral medicine cannot be taken. Doses must be prescribed

and monitored by the treating team.

Adrenal hormone treatment prevents adrenal crisis but does not treat brain or spinal cord disease.

For early, active cerebral ALD, an allogeneic hematopoietic stem cell transplant may slow or stop further inflammatory brain injury. This procedure replaces the blood-forming system using cells from a donor. It works best when MRI changes are limited and neurologic function is still largely preserved. It does not reliably restore skills already lost. Transplant can cause serious complications, including infection, organ injury, graft failure, and graft-versus-host disease, so evaluation occurs at an experienced center.

Elivaldogene autotemcel, sold as Skysona, is a gene therapy approved in the United States for certain boys ages 4 through 17 with early, active cerebral ALD who meet specific imaging and clinical criteria. It uses the patient's own blood-forming stem cells, which are modified to carry a working copy of the relevant gene. Treatment requires chemotherapy and specialized long-term monitoring. The prescribing information carries a boxed warning about blood cancers, including myelodysplastic syndrome and leukemia. Families considering this therapy need a detailed discussion of expected benefits, uncertainties, alternatives, and lifelong safety monitoring.

Stem cell transplant and gene therapy are not established treatments for the slowly progressive spinal cord symptoms of AMN. AMN care focuses on maintaining function and comfort. It may include physical and occupational therapy, stretching, exercise adapted to the person's abilities, mobility aids, fall prevention, and treatment of stiffness or nerve pain. Bladder, bowel, and sexual symptoms can be assessed and managed directly.

Lorenzo's oil is a mixture of fatty acids that can lower VLCFA levels in the blood. Evidence has not shown that it reverses neurologic symptoms. Its possible preventive role remains uncertain, and it should not replace MRI surveillance or established treatment. Strict dietary restriction of VLCFAs has also not been shown to control ALD because the body makes these fats internally.

Complications

Cerebral ALD may lead to progressive loss of vision, hearing, communication, movement, swallowing, and independent function. Seizures can occur. Early treatment may limit further injury, but advanced cerebral disease can cause profound disability.

AMN may cause increasing walking difficulty, falls, chronic pain, bladder infections, skin problems related to reduced mobility, and loss of independence. Rehabilitation and assistive

devices can reduce some of these effects.

Untreated adrenal insufficiency can lead to adrenal crisis, with dangerously low blood pressure, abnormal body salts, low blood sugar, or shock. Risk rises during vomiting, fever, major injury, or surgery if extra steroid medicine is not given as directed.

Stem cell transplant, gene therapy, chemotherapy, and long-term steroid treatment each have their own risks. The care team should explain the expected monitoring and warning signs for the specific treatment being considered.

ALD can also affect emotional health, education, work, relationships, and family planning. Psychological support, school services, social work, and connection with experienced patient organizations may help families manage these wider effects.

Follow up

Follow-up is lifelong, including for people without symptoms. Children and adolescents at risk for cerebral ALD generally need scheduled brain MRIs because imaging can reveal disease before clear symptoms appear. The timing changes with age and previous MRI findings. A specialist familiar with ALD should set the schedule.

Males need regular adrenal testing even when energy, appetite, and growth appear normal. Females usually do not require routine adrenal or brain MRI screening unless symptoms or other clinical concerns arise, but they should receive assessment for spinal cord symptoms as they get older.

Routine visits may review walking, balance, strength, pain, bladder and bowel function, school or work performance, mood, and caregiver needs. Report new learning problems, behavior changes, vision or hearing concerns, weakness, stiffness, falls, bladder symptoms, or persistent fatigue promptly rather than waiting for the next scheduled appointment.

People with adrenal insufficiency should carry medical identification and keep their emergency steroid plan available. Medication supplies and injection kits should be checked before travel and before they expire.

Sources

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