CONDITION

Metachromatic leukodystrophy

An inherited condition that damages the protective myelin around nerves in the brain and body.

WHAT IT IS
Inherited condition causing progressive loss of nerve insulation

BODY SYSTEM
Brain, spinal cord, and peripheral nerves

MAIN SYMPTOMS
Lost skills, weakness, stiffness, walking or thinking problems

WHAT CAUSES IT
Inherited gene changes affecting sulfatide breakdown

HOW IT IS DIAGNOSED
Enzyme, urine sulfatide, and genetic tests

MAIN TREATMENT
Gene therapy when eligible, plus supportive specialist care

CAN IT BE CURED?
No - treatments may slow progression

IS IT AN EMERGENCY?
Sometimes - breathing trouble or prolonged seizure

LONG-TERM OUTLOOK
Progressive disability, usually faster with earlier onset

Overview

Metachromatic leukodystrophy, often shortened to MLD, is a rare inherited condition affecting the nervous system. It damages myelin, the fatty protective layer around nerve fibres in the brain, spinal cord, and nerves elsewhere in the body.

Myelin helps electrical signals travel quickly and reliably. In MLD, fatty substances called sulfatides build up because the body cannot break them down properly. This buildup gradually damages myelin and the cells that make it.

MLD can begin in infancy, childhood, adolescence, or adulthood. Earlier-onset forms usually progress more quickly. Later-onset forms may develop over years and can first appear as changes in school performance, behaviour, mood, or thinking.

The condition is serious because nerve damage can affect movement, swallowing, communication, vision, hearing, and thinking. Early diagnosis matters. Some treatments are most helpful before symptoms begin or while symptoms are still limited.

Symptoms

Symptoms depend strongly on the age at which MLD begins. They often become more noticeable over time. A child or adult may lose abilities they previously had rather than simply being slow to gain new ones.

In late-infantile MLD, early signs may include difficulty walking, frequent falls, muscle weakness, or a change in muscle tone. A child may stop gaining movement skills and then lose skills such as standing, walking, or sitting without support.

Juvenile MLD can first cause problems with schoolwork, attention, behaviour, coordination, or walking. Movement difficulties and loss of thinking skills usually become clearer as the condition progresses.

Adult MLD may begin with changes in personality, judgement, work performance, memory, or mental health. Movement problems, weakness, stiffness, poor balance, and loss of bladder control can develop later. These symptoms can resemble more common neurological or mental health conditions, so diagnosis may take time.

Possible symptoms across the different forms include:

These symptoms have many possible causes. Having one or more does not mean that you or your child has MLD.

- Loss of walking, speaking, self-care, or learning skills
- Muscle weakness, stiffness, spasms, or unusually low muscle tone
- Poor balance, clumsiness, falls, or abnormal walking
- Numbness or reduced reflexes from damage to peripheral nerves
- Changes in memory, concentration, behaviour, or personality
- Speech, vision, or hearing difficulties
- Trouble chewing or swallowing
- Seizures

Causes and risk factors

Most MLD is caused by changes in both copies of the ARSA gene. This gene provides instructions for making arylsulfatase A, an enzyme that helps break down sulfatides. An enzyme is a protein that carries out a chemical task in the body.

When arylsulfatase A activity is very low, sulfatides collect in the nervous system and some other organs. Much less often, MLD results from changes in the PSAP gene that cause a shortage of saposin B, a protein needed for the same breakdown process.

MLD is usually inherited in an autosomal recessive pattern. This means an affected person received one altered gene copy from each biological parent. Parents are usually healthy carriers because their other copy works normally.

When both parents carry an ARSA change linked to MLD, each pregnancy has:

These chances restart with every pregnancy. They do not change based on the outcome of an earlier pregnancy.

The main risk factor is having biological parents who carry relevant gene changes. MLD is not caused by parenting, diet, infection, injury, or anything someone did during pregnancy.

- A 1 in 4 chance of an affected child
- A 1 in 2 chance of a child who is an unaffected carrier
- A 1 in 4 chance of a child who is neither affected nor a carrier

Diagnosis

Diagnosis usually combines enzyme testing, measurement of sulfatides, and genetic testing. No single result should always be interpreted alone.

A blood or skin-cell test can measure arylsulfatase A activity. Very low activity supports the diagnosis, but some healthy people have ARSA pseudodeficiency . This means laboratory testing shows low enzyme activity even though the person does not develop MLD.

A urine test can look for raised sulfatide levels. Genetic testing can identify changes in both copies of ARSA. If arylsulfatase A activity is normal but MLD is still suspected, testing may look for PSAP changes and saposin B deficiency.

Other assessments help show how the nervous system is affected. These may include:

MRI findings can support the diagnosis but do not usually confirm MLD by themselves.

Once one family member is diagnosed, close biological relatives may be offered testing. Testing siblings promptly can be especially important because treatment may work best before clear symptoms develop.

- MRI scans to look for characteristic changes in the brain's white matter
- Nerve-conduction studies to measure signals in peripheral nerves
- Movement, speech, swallowing, vision, hearing, and developmental assessments
- Psychological or cognitive testing for changes in learning and thinking

Treatment and management

Care is usually coordinated through a specialist centre experienced in inherited metabolic and neurological conditions. Treatment choices depend on age at onset, current symptoms, test results, and how much nerve damage has already occurred.

Atidarsagene autotemcel is a one-time gene therapy made from a child's own blood-forming stem cells. The cells are collected, given a working copy of the ARSA gene in a laboratory, and returned after chemotherapy prepares the bone marrow.

In the United States, this therapy is approved for certain children with presymptomatic late-infantile or early-juvenile MLD, and for some children with early symptomatic early-juvenile MLD. Eligibility and availability differ between countries. It is not expected to restore skills already lost, and it has important risks related to stem-cell collection, chemotherapy, infection, and blood-cell recovery.

A donor stem-cell transplant may be considered in selected people, particularly with juvenile or adult forms before major neurological decline. Its benefits are limited once symptoms are advanced, and it carries serious risks. It is generally not able to stop rapidly progressing late-infantile MLD after symptoms are established.

Supportive treatment remains central at every stage. It may include:

Palliative care is not limited to the end of life. It can be introduced early to manage symptoms, support comfort, and help families make decisions that fit their priorities.

- Physiotherapy and equipment to support movement and positioning
- Medicines and stretching plans for stiffness, spasms, pain, or seizures
- Speech and communication support
- Swallowing assessment and nutrition support
- Feeding through a tube when eating is unsafe or inadequate
- Respiratory care and help clearing mucus
- Psychological, educational, social, and palliative care

Complications

Progressive damage to the brain and peripheral nerves can lead to severe movement and communication disability. Some people eventually need full support with mobility and personal care.

Swallowing problems can allow food, drink, or saliva to enter the lungs. This is called aspiration and can cause chest infections. Reduced mobility and weak coughing can also make it harder to clear mucus.

Other possible complications include malnutrition, dehydration, constipation, pain, joint tightening, pressure injuries, seizures, and repeated respiratory infections. Gallbladder problems can occur because sulfatides may also collect there.

Changes in judgement or mental health can affect safety, relationships, school, or employment in later-onset MLD. Families and caregivers may also experience major practical and emotional strain.

Regular reviews are used to identify these problems early and adjust support. The review schedule is individual and may become more frequent as needs change.

Prevention

MLD cannot be prevented through diet, exercise, vaccination, or lifestyle choices because it is inherited.

Genetic counselling can help people understand how MLD is passed on and what testing options are available. Carrier testing may be possible for adult relatives once the family's gene changes are known.

People planning a pregnancy may choose to discuss prenatal testing or testing embryos created through in vitro fertilisation. These are personal options, not requirements. A genetics team can explain their accuracy, limits, timing, and practical implications without directing the decision.

Newborn screening for MLD is being studied or introduced in some places, but it is not universally available. Its purpose is early detection rather than prevention.

Living with it and what to expect

MLD is progressive, meaning nervous-system function tends to worsen over time. The pace is

closely linked to when symptoms first appear, but it is not identical for everyone.

Late-infantile MLD usually progresses over months to a few years. Children may lose walking, sitting, speech, and safe swallowing. They can remain aware of familiar voices, touch, music, and comfort even when they cannot respond in their previous ways.

Juvenile MLD often progresses over several years. School, behaviour, and walking may be affected before more extensive support is needed. Adult MLD may change more slowly, sometimes over many years, although significant cognitive and physical disability can develop.

Gene therapy or stem-cell transplantation may slow or prevent some progression when used at the right stage. They cannot reliably reverse established nerve damage, and continued follow-up is needed after treatment.

Daily life may involve mobility equipment, adapted communication, feeding support, home modifications, and help at school or work. Care plans often focus on preserving comfort, participation, relationships, and meaningful activities rather than only measuring lost skills.

Future planning can include decisions about nutrition, respiratory support, symptom control, emergency care, finances, and caregiver support. These conversations can happen gradually and should reflect the affected person's values whenever possible.

When to get medical help

Arrange a routine medical review if you notice unexplained loss of previously learned movement, language, school, work, or self-care skills. Ongoing falls, increasing stiffness, swallowing changes, or new behaviour and thinking problems also need assessment. These concerns are usually not emergencies, but they should not be ignored.

If MLD has already been diagnosed, contact the care team promptly about worsening swallowing, repeated coughing during meals, weight loss, new seizures, increasing pain, or changes in breathing and mucus clearance.

Seek urgent medical help for a first seizure, a major sudden decline, signs of dehydration, or symptoms of a chest infection in someone who has swallowing or coughing difficulties.

Call emergency services for:

Follow an existing emergency plan if the specialist team has provided one.

- Severe trouble breathing, blue or grey lips, or choking that does not clear
- A seizure lasting five minutes or longer
- Repeated seizures without recovery between them

- Unresponsiveness or a sudden inability to wake normally

Common questions

Is metachromatic leukodystrophy always inherited?

Almost always. Most people inherit two altered ARSA gene copies, one from each biological parent. Rare cases involve PSAP gene changes affecting saposin B. Parents who carry one altered copy usually have no symptoms.

Can metachromatic leukodystrophy be cured?

There is no treatment that reliably removes established nerve damage or cures every form of MLD. Gene therapy can change the course for some eligible children treated before symptoms or very early after they begin. Donor stem-cell transplantation may help selected people with slower-onset forms.

How quickly does MLD progress?

Earlier-onset forms usually progress faster. Late-infantile MLD may change over months, while juvenile and adult forms may progress over years. Gene changes, age at first symptoms, and treatment timing all influence the course.

Can someone with low arylsulfatase A have MLD without symptoms?

Low enzyme activity alone does not confirm MLD. Some healthy people have ARSA pseudodeficiency and never develop the condition. Urine sulfatide testing, genetic results, symptoms, and imaging help distinguish pseudodeficiency from MLD.

Can adults develop metachromatic leukodystrophy?

Yes. Adult-onset MLD may first appear as changes in work performance, judgement, mood, personality, or memory. Problems with balance, stiffness, weakness, or bladder control may follow.

Should brothers and sisters be tested after a diagnosis?

Testing is often offered because full siblings may have inherited the same gene changes. Rapid testing is especially important for children without symptoms, since eligibility for disease-modifying treatment can depend on starting before substantial nerve damage occurs.

Sources

- National Institute of Neurological Disorders and Stroke: Metachromatic Leukodystrophy



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