CONDITION

Alexander disease

Learn how Alexander disease affects the brain and nervous system, including its symptoms, genetic cause, diagnosis, supportive treatment, and follow-up care.

WHAT IT IS
Rare inherited leukodystrophy affecting the brain and spinal cord

BODY SYSTEM
Nervous system

MAIN SYMPTOMS
Developmental delays, seizures, muscle stiffness, swallowing difficulties

WHAT CAUSES IT
Inherited GFAP gene variant

HOW IT IS DIAGNOSED
Genetic testing for a pathogenic GFAP variant

MAIN TREATMENT
Supportive care and symptom management

CAN IT BE CURED?
No, no approved therapy reverses it

IS IT AN EMERGENCY?
Sometimes, with severe trouble breathing

LONG-TERM OUTLOOK
Gradual progression with a widely varying course

Overview

Alexander disease is a rare, inherited disorder that mainly affects the brain and spinal cord. It is often described as a leukodystrophy , a group of conditions that damage the brain's white matter. White matter contains nerve fibers and the myelin that helps signals travel through the nervous system.

Unlike many leukodystrophies, Alexander disease begins in astrocytes . These are cells that support nerve cells, help control the brain's chemical environment, and contribute to the health of myelin. Changes in a protein called glial fibrillary acidic protein, or GFAP, cause astrocytes to function abnormally.

Alexander disease can begin at any age. Symptoms that start in infancy or early childhood often differ from those beginning in adolescence or adulthood. However, there is substantial

overlap, and the age when symptoms begin does not perfectly predict their course.

Doctors sometimes group the condition into two broad patterns. Type I usually begins earlier and often involves developmental problems, seizures, stiffness, and an enlarged head. Type II may begin later and more often affects speech, swallowing, coordination, breathing during sleep, and control of automatic body functions. These categories are helpful descriptions rather than strict rules.

Alexander disease matters because it can gradually affect movement, communication, nutrition, breathing, learning, and independence. The rate of change varies widely. Although there is currently no approved treatment that corrects the underlying genetic change, coordinated medical and supportive care can manage symptoms and help maintain comfort, safety, and participation in daily life.

Symptoms

Symptoms depend on which areas of the nervous system are affected. They may appear over months or years, and not every person develops every feature.

Infants and young children may have developmental delays or lose skills they previously gained. Some have difficulty sitting, walking, speaking, or learning. An unusually rapid increase in head size, called macrocephaly , can occur, although it is not present in everyone.

Other possible childhood symptoms include:

People whose symptoms begin later may have weakness, stiffness, poor balance, or tremor. Speech can become slow, soft, or unclear. Swallowing may become difficult, which can lead to coughing during meals or food entering the airway.

The condition may also affect the lower brainstem and upper spinal cord. These areas help control breathing, swallowing, and automatic functions such as blood pressure. Possible symptoms include sleep apnea, abnormal sweating, bladder problems, constipation, faintness when standing, or changes in body temperature control.

Some adults first notice repeated vomiting, sleep problems, changes in speech, or difficulty walking. Thinking and memory may remain relatively preserved in some people, while others develop cognitive or behavioral changes.

Symptoms alone cannot confirm Alexander disease. Many neurological conditions can cause similar problems, so a medical evaluation is important.

- Seizures
- Muscle stiffness or tightness, known as spasticity

- Weakness or limited coordination
- Feeding problems, vomiting, or poor growth
- Problems with balance and walking
- Changes in alertness or behavior
- Fluid buildup in the brain, called hydrocephalus

Causes and risk factors

Alexander disease is caused by a disease-causing change, also called a pathogenic variant, in the GFAP gene. This gene provides instructions for making GFAP, a structural protein found mainly in astrocytes.

The altered protein accumulates within astrocytes and contributes to clumps called Rosenthal fibers . These changes interfere with the cells' ability to support the brain and spinal cord. The effects can include inflammation, stress within cells, and damage to white matter.

Alexander disease follows an autosomal dominant inheritance pattern. This means one altered copy of the GFAP gene is enough to cause the condition. Most affected people have a new genetic change that occurred in the egg, sperm, or early embryo. In those cases, neither parent has the disease-causing variant in routine testing.

A person who carries a pathogenic GFAP variant can pass it to a child. For each pregnancy, an affected parent has a 1 in 2 chance of passing on the variant. The severity and age at onset can differ even among relatives with the same genetic change.

When a child has a new variant that is not detected in either parent, the chance of the same parents having another affected child is usually low but is not always zero. Rarely, a parent may have the variant in only some egg or sperm cells. A genetics professional can explain recurrence risk based on the family's test results.

Alexander disease is not caused by parenting, diet, an infection, or an exposure during pregnancy. It is not contagious.

Diagnosis

Diagnosis usually begins with a neurological examination and a detailed history. The clinician may ask about development, seizures, walking, muscle stiffness, swallowing, sleep, bladder or bowel symptoms, and similar problems in relatives.

Magnetic resonance imaging, or MRI, provides detailed pictures of the brain and sometimes the spinal cord. MRI findings vary with age and disease pattern. They may include changes in the frontal white matter, tissue around the brain's fluid-filled spaces, the basal ganglia or thalamus, the brainstem, and the upper spinal cord.

In later-onset disease, MRI may show shrinkage of the medulla and upper spinal cord while tissue higher in the brainstem is relatively preserved. Radiologists sometimes call this a "tadpole appearance." MRI findings can strongly suggest Alexander disease, but genetic testing is generally used to confirm it.

Genetic testing looks for a pathogenic variant in GFAP, usually using a blood or saliva sample. Testing may examine GFAP alone or include it in a panel of genes linked to leukodystrophies, movement disorders, epilepsy, or hereditary spasticity. Broader testing, such as exome or genome sequencing, may be considered when the diagnosis remains unclear.

Not every genetic result gives a definite answer. A variant of uncertain significance means there is not enough evidence to know whether a specific change causes disease. Such a result should be interpreted along with symptoms, MRI findings, family history, and sometimes testing of relatives.

Before genetic testing became available, diagnosis could require examination of brain tissue for Rosenthal fibers. A brain biopsy is now rarely needed when clinical, MRI, and genetic findings establish the diagnosis.

Treatment and management

There is currently no approved therapy that reverses Alexander disease or repairs the GFAP gene change. Treatment focuses on specific symptoms, prevention of avoidable complications, and support for the person and family. Research into treatments that reduce abnormal GFAP production is ongoing, but experimental treatments are not the same as established care.

Management often involves a neurologist and other specialists based on the person's needs. Care may include:

A swallowing assessment can help determine whether food or liquid is entering the airway. Changes in food texture, seating, pacing, or feeding technique may improve safety. If eating by mouth no longer provides adequate nutrition or becomes unsafe, clinicians may discuss feeding through a tube. This is an individualized decision that should consider medical needs, comfort, and the person's goals.

Mobility equipment can help conserve energy and reduce falls. Splints, supportive seating,

standing devices, walkers, or wheelchairs may improve positioning and participation. Regular stretching may help limit painful tightening of muscles and joints.

Communication support should begin before speech becomes severely limited. Picture boards, tablets, eye-gaze systems, or other assistive devices may help a person continue to express choices and take part in decisions.

Families may also benefit from genetic counseling, social work support, school planning, respite services, and palliative care. Palliative care is not limited to end-of-life care. It can be added at any stage to address symptoms, stress, decision-making, and quality of life.

- Anti-seizure treatment for epilepsy
- Physical therapy to support mobility, positioning, and flexibility
- Occupational therapy for daily activities and adaptive equipment
- Speech therapy for communication and swallowing
- Treatment of muscle stiffness, pain, or spasms
- Nutrition support when chewing, swallowing, or growth is affected
- Sleep evaluation and breathing support for sleep apnea
- Management of constipation, bladder symptoms, vomiting, or blood pressure changes
- Educational and developmental services for children

Complications

Potential complications depend on disease severity and the areas of the nervous system involved.

Swallowing problems can cause dehydration, poor nutrition, or aspiration , which means food, liquid, or saliva enters the airway. Aspiration can lead to lung infections. Weak coughing or impaired breathing control may make it harder to clear airway secretions.

Reduced movement and ongoing spasticity can lead to falls, joint stiffness, abnormal posture, pressure injuries, and pain. People with limited mobility may also need monitoring for loss of bone strength.

Seizures may recur or, less often, become prolonged. Sleep apnea can cause disrupted sleep, daytime fatigue, morning headaches, or strain on the heart and lungs if it is not recognized and treated.

Some people develop worsening bladder or bowel control, severe vomiting, or unstable blood pressure. Hydrocephalus may increase pressure within the skull and may require specialist

treatment.

The condition can also affect emotional health, family routines, education, employment, and caregiving needs. Support for caregivers is an important part of long-term management.

Follow up

Follow-up should be tailored to symptoms and how quickly they are changing. Routine visits may review development, mobility, seizures, muscle tone, pain, nutrition, swallowing, communication, sleep, breathing, bladder and bowel function, and emotional well-being.

Repeat MRI is not automatically needed at every visit. A neurologist may recommend imaging when symptoms change, when the diagnosis is uncertain, or when the result could affect care. Medication and equipment should be reviewed as a person grows or their abilities change.

Contact the treating clinician promptly for new or gradually worsening swallowing problems, repeated coughing with meals, weight loss, increased falls, changes in seizure pattern, new weakness, worsening sleep symptoms, or loss of previously stable abilities.

Seek urgent or emergency care for:

People with known seizures or breathing problems should have an emergency plan developed with their clinical team. Caregivers, school staff, and other regular helpers should know where to find it.

- Severe trouble breathing, blue or gray lips, or choking that does not clear
- A seizure lasting about five minutes or longer, unless the person's seizure plan gives different instructions
- Repeated seizures without recovery between them
- Sudden inability to wake, severe confusion, or a major unexpected neurological change
- Signs of serious dehydration or possible aspiration with breathing difficulty

Sources

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