CONDITION

Argininemia

Learn how argininemia affects the urea cycle, including its symptoms, inheritance, diagnosis, treatment, emergency warning signs, and long-term follow-up.

WHAT IT IS
Rare inherited urea cycle disorder

BODY SYSTEM
Metabolism and nervous system

MAIN SYMPTOMS
Muscle stiffness, difficulty walking, developmental problems, seizures

WHAT CAUSES IT
Inherited ARG1 gene changes

HOW IT IS DIAGNOSED
Genetic testing and arginase enzyme testing

MAIN TREATMENT
Protein-controlled diet and metabolic medicines

CAN IT BE CURED?
Sometimes - liver transplantation corrects enzyme deficiency

IS IT AN EMERGENCY?
Sometimes - severe confusion or loss of consciousness

LONG-TERM OUTLOOK
Variable, with progressive neurological injury if poorly controlled

Overview

Argininemia is a rare inherited disorder that affects how the body removes nitrogen from protein. It is also called arginase 1 deficiency or ARG1 deficiency.

When the body breaks down protein, it produces ammonia. Ammonia is toxic at high levels, especially to the brain. The liver normally converts ammonia into urea through a series of chemical reactions called the urea cycle. Urea then leaves the body in urine.

People with argininemia have too little working arginase 1, the enzyme responsible for the final step of the urea cycle. This causes arginine, an amino acid, to build up in the blood. Other substances made from arginine may also accumulate and affect the nervous system.

Argininemia often differs from other urea cycle disorders. Severe ammonia buildup can occur,

but it is less common than in some related conditions. Instead, many affected children gradually develop muscle stiffness, difficulty walking, developmental problems, or seizures. Symptoms often begin between infancy and early childhood, although the timing and severity vary.

Early diagnosis matters because treatment can lower arginine, reduce the risk of ammonia buildup, and support development and mobility. Treatment is usually coordinated by a metabolic specialist and continues throughout life.

Symptoms

Babies with argininemia may appear healthy at birth. Symptoms can develop slowly, so early changes may be mistaken for other developmental or movement conditions.

Possible symptoms include:

The progressive muscle stiffness is called spasticity . It occurs when the brain and spinal cord have difficulty controlling muscle tone. Spasticity may begin in the legs and later affect the arms or other parts of the body.

Some people develop episodes of hyperammonemia , meaning that ammonia in the blood becomes too high. Illness, prolonged fasting, surgery, or another source of physical stress may trigger an episode.

Repeated vomiting, unusual sleepiness, confusion, rapid breathing, severe behavior changes, a seizure, or loss of consciousness may be signs of dangerously high ammonia. These symptoms require emergency medical evaluation. A person with a known urea cycle disorder should follow their emergency or sick-day plan while seeking care.

- Stiff or tight muscles, especially in the legs
- Walking on the toes, frequent falls, or difficulty walking
- Delayed motor skills, such as sitting or walking later than expected
- Loss of previously learned skills
- Learning or intellectual difficulties
- Slow growth
- Poor coordination
- Tremor or uncontrolled movements
- Seizures

- Irritability, sleepiness, vomiting, or poor appetite

Causes and risk factors

Argininemia is caused by disease-causing changes in the `ARG1` gene. This gene provides instructions for making arginase 1, an enzyme found mainly in the liver. Arginase 1 converts arginine into urea and ornithine during the final step of the urea cycle.

When arginase 1 does not work well enough, arginine and related chemicals build up. The exact reason these substances cause nervous system injury is not fully understood. High arginine and compounds called guanidino compounds are thought to contribute.

Argininemia follows an autosomal recessive inheritance pattern. A person must inherit one altered `ARG1` gene from each biological parent to have the condition. The parents are usually healthy carriers.

When both parents are carriers, each pregnancy has:

These chances are the same for each pregnancy. Argininemia is not caused by parenting, diet during pregnancy, or anything the affected person did.

The main risk factor is having biological parents who carry an altered `ARG1` gene. A known family history increases the chance of early identification, but the condition may occur in a family with no previous diagnosis.

In someone who has argininemia, infection, fasting, dehydration, surgery, or other physical stress can increase protein breakdown within the body. This may raise ammonia and worsen metabolic control.

- A 25% chance that the child will have argininemia
- A 50% chance that the child will be an unaffected carrier
- A 25% chance that the child will inherit neither altered copy

Diagnosis

Some newborn screening programs test for elevated arginine using a small blood sample collected after birth. Newborn screening practices vary by location. Screening can identify babies before symptoms develop, but it is not a final diagnosis.

Arginine may rise gradually, so newborn screening may not identify every affected baby. A normal result does not completely rule out argininemia when a child later develops concerning

symptoms.

Testing after an abnormal newborn screen or clinical concern may include:

Doctors interpret these results together. Elevated arginine can have more than one explanation, and confirmation by a metabolic or genetics team is important.

After diagnosis, close biological relatives may be offered genetic testing. A genetic counselor can explain carrier testing, testing during pregnancy, and reproductive options. Testing an at-risk newborn shortly after birth may allow treatment to begin before symptoms appear.

- Plasma amino acid testing: Measures amino acids in the blood. Argininemia usually causes a marked elevation in arginine.
- Blood ammonia: Checks for ammonia buildup. A normal ammonia level at one point does not exclude the condition.
- Urine testing: May measure orotic acid and other substances related to the urea cycle.
- Liver and metabolic tests: Help assess the effects of illness and rule out other causes.
- Genetic testing: Looks for disease-causing changes in both copies of the `ARG1` gene.
- Enzyme testing: Measures arginase activity in certain cells and may be used when genetic results are unclear.

Treatment and management

Treatment aims to lower arginine and other nitrogen-containing waste products, prevent high ammonia, and protect growth, movement, and development. Care is usually directed by a metabolic physician and dietitian with experience in urea cycle disorders.

A protein-controlled eating plan is a central part of treatment. Protein provides amino acids needed for growth, tissue repair, and many body functions. However, breaking down too much protein can increase arginine and nitrogen waste.

The appropriate amount of protein depends on age, growth, health, laboratory results, and other factors. Protein should not be severely restricted or removed without specialist guidance. Too little protein can cause poor growth, muscle loss, and the breakdown of the body's own tissues, which can also increase ammonia.

Some people use a specialized medical formula that supplies essential amino acids and nutrients while limiting arginine. Vitamins, minerals, or additional calories may be recommended when needed. A metabolic dietitian can help families plan meals that meet nutritional needs.

Medicines called nitrogen scavengers may be used. These medicines provide alternative ways for the body to remove nitrogen instead of relying entirely on the urea cycle. Examples include sodium benzoate, sodium phenylbutyrate, and glycerol phenylbutyrate. The choice of medicine depends on the person's clinical needs and local availability.

Pegzilarginase is an enzyme replacement that helps break down arginine. It is authorized for certain patients in some countries as an addition to standard treatment. Availability and eligibility vary by location, so families should discuss it with their metabolic team.

A written sick-day plan is important. During illness, the body may break down its own protein, even when a person is eating less. The plan may include guidance about calories, fluids, prescribed medicines, laboratory testing, and when to go to the hospital. It should be shared with caregivers, schools, and local emergency departments when appropriate.

An acute hyperammonemia episode is treated in a hospital. Treatment may include intravenous fluids and calories, medicines that remove nitrogen, and temporary changes in protein intake. Very high ammonia may require dialysis, a procedure that rapidly removes ammonia from the blood.

Supportive treatment can address the neurological effects of argininemia. Physical therapy may help maintain strength, flexibility, balance, and mobility. Occupational therapy can support daily activities. Speech, learning, and developmental services may also be useful. Specialists can treat seizures, spasticity, contractures, and orthopedic problems.

Liver transplantation may be considered for selected patients. A transplanted liver supplies working arginase 1 and can correct the underlying liver enzyme deficiency. However, transplantation has major risks and requires lifelong medical care. It may not reverse neurological injury that has already occurred. The potential benefits and risks require detailed discussion with metabolic and transplant specialists.

Complications

Without adequate metabolic control, argininemia can cause progressive injury to the nervous system. Muscle stiffness may worsen and lead to difficulty walking, loss of mobility, painful spasms, or fixed shortening of muscles and joints. This fixed shortening is called a contracture.

Developmental, learning, or behavioral difficulties may affect school and daily activities. Some people develop recurrent seizures. Growth and nutrition can also be affected.

Hyperammonemia can cause brain swelling and serious neurological injury, particularly when treatment is delayed. Although severe ammonia episodes are not as typical in argininemia as in some other urea cycle disorders, they remain an important medical risk.

Liver enlargement or abnormal liver blood tests may occur. Long-term complications vary widely, and blood arginine or ammonia results do not always predict an individual person's neurological symptoms.

Follow up

Argininemia requires lifelong follow-up with a metabolic team. Routine visits usually review growth, nutrition, development, mobility, medicines, and the ability to follow the treatment plan. Blood tests may include amino acids, ammonia, nutritional markers, and liver tests. The timing of testing is individualized.

Children may need regular developmental, neurological, physical therapy, and school assessments. Monitoring for worsening spasticity, contractures, seizures, pain, or reduced mobility can help the care team respond early. Adults may need support as they transition from pediatric to adult metabolic services.

Contact the metabolic team promptly for poor intake, repeated vomiting, unusual sleepiness, a new seizure, or a significant change in behavior or movement. The team should also be notified before planned surgery or a procedure that requires fasting.

Emergency care is needed for severe confusion, marked difficulty waking, rapid or unusual breathing, repeated seizures, collapse, or loss of consciousness. Tell emergency clinicians about the urea cycle disorder and provide the person's emergency letter or sick-day plan if available.

Routine follow-up should also include review of family testing and genetic counseling when relevant. People planning a pregnancy can discuss inheritance, testing options, nutrition, and metabolic care before conception.

Sources

- American College of Medical Genetics and Genomics. Newborn Screening ACT Sheet: Increased Arginine-Arginase Deficiency . ACMG; 2022.
- European Medicines Agency. Loargys (pegzilarginase): European Public Assessment Report . EMA; first authorized 2023.
- Häberle J, Burlina A, Chakrapani A, Dixon M, Karall D, Lindner M, et al. Suggested guidelines for the diagnosis and management of urea cycle disorders: First revision. Journal of Inherited Metabolic Disease . 2019;42(6):1192-1230. doi:10.1002/jimd.12100.

- National Center for Biotechnology Information. Arginase Deficiency . In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews . University of Washington, Seattle.
- National Library of Medicine. Arginase Deficiency . MedlinePlus Genetics. U.S. National Institutes of Health.