CONDITION

Arginase deficiency

Learn how arginase deficiency 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

MAIN SYMPTOMS
Leg stiffness, difficulty walking, developmental delay, seizures

WHAT CAUSES IT
Inherited ARG1 gene changes

HOW IT IS DIAGNOSED
ARG1 genetic testing or arginase enzyme testing

MAIN TREATMENT
Protein-controlled diet and metabolic therapies

CAN IT BE CURED?
Sometimes - liver transplantation corrects metabolic defect

IS IT AN EMERGENCY?
Sometimes - difficulty waking or loss of consciousness

LONG-TERM OUTLOOK
Earlier control may reduce injury, but disability can progress

Overview

Arginase deficiency is a rare inherited condition that affects how the body removes nitrogen from protein. It is also called arginase 1 deficiency, ARG1 deficiency, or hyperargininemia.

When the body breaks down protein, it produces ammonia. Ammonia is toxic at high levels. The liver normally changes ammonia into urea, which leaves the body in urine. This process is called the urea cycle .

Arginase is the final enzyme in the urea cycle. It breaks down an amino acid called arginine and helps form urea. In arginase deficiency, the enzyme does not work well enough. Arginine and related substances can build up in the blood and tissues. Ammonia may also rise, particularly during illness, fasting, or other physical stress.

Arginase deficiency differs from many other urea cycle disorders. Severe ammonia problems in the newborn period are less common. Many children initially appear healthy but later develop muscle stiffness, difficulty walking, slowed growth, or developmental concerns. Symptoms often begin in early childhood, although the age and pattern vary.

Early diagnosis matters because treatment can lower arginine and reduce the risk of further nervous system injury. Treatment usually requires lifelong care from a metabolic specialist and dietitian.

Symptoms

Symptoms may develop gradually. A child may meet early milestones and then make progress more slowly, lose skills, or develop increasing stiffness in the legs. People identified through newborn screening may begin treatment before clear symptoms appear.

Common features can include:

Spasticity often affects the legs more than the arms. Without effective control of the condition, stiffness may worsen and make independent walking difficult.

Some people develop hyperammonemia , meaning too much ammonia in the blood. Symptoms may include vomiting, unusual sleepiness, confusion, poor coordination, or changes in behavior. A person with arginase deficiency can become unwell quickly during an infection, after prolonged fasting, or when unable to follow the usual nutrition plan.

Seek urgent medical advice if a person with known or suspected arginase deficiency develops repeated vomiting, unusual drowsiness, new confusion, worsening balance, or marked behavior changes.

Call emergency services for difficulty waking, a seizure lasting longer than directed in the person's emergency plan, trouble breathing, collapse, or loss of consciousness. These symptoms can have several causes, but they require immediate assessment. Tell the emergency team about the urea cycle disorder and provide the person's emergency letter if available.

- Stiff or tight leg muscles, known as spasticity
- Walking on the toes, an unsteady walk, or frequent falls
- Difficulty with balance and coordination
- Developmental delay or learning difficulties
- Loss of previously learned movement or communication skills

- Slowed growth or a smaller-than-expected head size
- Tremor or other unusual movements
- Seizures
- Irritability, behavior changes, or reduced alertness
- Nausea, vomiting, poor appetite, or avoidance of high-protein foods

Causes and risk factors

Arginase deficiency is caused by disease-causing changes in the ARG1 gene. This gene provides instructions for making the arginase 1 enzyme, mainly in the liver.

The condition has an autosomal recessive inheritance pattern. This means a person usually has a disease-causing ARG1 change in both copies of the gene. The parents are typically carriers, with one changed copy each. Carriers usually do not have symptoms.

When both biological parents are carriers, each pregnancy has:

These chances are the same for each pregnancy. Genetic testing can clarify the changes present in a family. A genetic counselor can explain testing options for siblings, other relatives, future pregnancies, and adults planning a family.

The main risk factor is having biological parents who carry an ARG1 gene change. The condition is not caused by something a parent ate, did, or was exposed to during pregnancy.

Illness, fever, surgery, prolonged fasting, dehydration, or a sudden increase in protein intake may trigger metabolic problems in someone who already has the condition. These factors do not cause arginase deficiency, but they can make it harder for the body to control ammonia and arginine.

- A 25% chance that the child will have arginase deficiency
- A 50% chance that the child will be an unaffected carrier
- A 25% chance that the child will inherit neither familial change

Diagnosis

Arginase deficiency may be identified through newborn screening, evaluation of symptoms, or family testing. Newborn screening programs differ by location. Where screening includes arginase deficiency, it generally looks for elevated arginine in a dried blood sample.

A normal newborn screen does not always exclude the condition. Arginine may not yet be high enough during the first days of life, and screening practices vary. Symptoms or a known family history still require medical evaluation.

Diagnostic testing may include:

An elevated arginine result by itself is not enough to diagnose the condition. Clinicians interpret it with symptoms, repeat laboratory results, nutrition, liver function, and genetic or enzyme testing.

Assessment may involve a metabolic physician, genetic counselor, dietitian, neurologist, and physical or occupational therapist. Testing of close relatives may be offered once the familial gene changes are known.

- Plasma amino acid testing: This measures amino acids in the blood. Persistently high arginine is an important finding.
- Blood ammonia testing: Ammonia may be normal or mildly elevated between episodes but can rise during illness.
- Urine testing: Urine amino acids and orotic acid may help assess the urea cycle and distinguish among related disorders.
- Liver and metabolic blood tests: These help evaluate the effects of illness and look for other explanations.
- ARG1 genetic testing: Finding disease-causing changes in both copies of the gene can confirm the diagnosis.
- Enzyme testing: Measurement of arginase activity in red blood cells may be used when genetic results are unclear or unavailable.

Treatment and management

Treatment aims to keep arginine and ammonia in safer ranges while providing enough nutrition for growth, muscle health, and daily function. Plans are individualized by a metabolic team.

A protein-controlled diet is a central part of care. Because arginine comes from dietary protein and is also made by the body, protein is limited but not eliminated. Too little protein can cause poor growth, muscle loss, and nutritional deficiencies. A metabolic dietitian can determine how much natural protein is appropriate and adjust the plan over time.

Some people use a specialized amino acid formula. These medical foods provide essential amino acids and other nutrients while limiting arginine. Vitamins, minerals, and calories must also be adequate. Families should not make major protein changes without the metabolic

team.

Nitrogen-scavenging medicines may be prescribed. These medicines provide other pathways for removing nitrogen when the urea cycle cannot handle it effectively. Examples include sodium phenylbutyrate, glycerol phenylbutyrate, or sodium benzoate in settings where they are used. The choice depends on age, clinical needs, local approval, and specialist guidance.

Pegzilarginase is an enzyme replacement therapy that lowers arginine by supplying an alternative form of arginase. It is authorized for certain patients in some countries and is used alongside standard metabolic care. Availability and approved ages differ by region. A specialist can explain whether it is an option.

Management also may include:

Every patient should have a written illness or emergency plan. During fever, vomiting, poor intake, or surgery, the body may break down its own protein and release more nitrogen. The plan may call for rapid contact with the metabolic team, temporary nutrition changes, laboratory testing, or hospital care. It should be followed instead of improvising a high-sugar or low-protein regimen at home.

In a metabolic crisis, hospital treatment may include intravenous fluids containing calories, medicines that remove nitrogen, close ammonia monitoring, and treatment of the trigger. Dialysis may be needed when ammonia is dangerously high or does not fall promptly with initial treatment.

Liver transplantation can provide working arginase enzyme and correct the underlying liver-based metabolic defect. It may prevent future hyperammonemia and improve biochemical control. However, it is major surgery with lifelong implications, and it may not reverse nervous system injury that has already occurred. A transplant center and metabolic team can discuss potential benefits and risks.

- Physical and occupational therapy for mobility and daily activities
- Stretching, braces, mobility aids, or other treatment for spasticity
- Speech, learning, and developmental support
- Standard antiseizure treatment when seizures occur
- School accommodations and psychosocial support

Complications

The main long-term concern is progressive injury to the nervous system. Persistently high arginine and related compounds may contribute to increasing leg stiffness, weakness, poor

coordination, and loss of walking ability.

Muscle tightness can lead to fixed shortening around a joint, called a contracture . Contractures may cause pain, interfere with positioning, and make dressing or walking harder. Hip, spine, and foot problems can develop when muscle forces remain uneven.

Learning difficulties, intellectual disability, speech problems, and seizures may also occur. The degree of disability varies. Earlier and sustained metabolic control may reduce further injury, but treatment cannot always restore skills that have been lost.

Hyperammonemia is less typical than in some other urea cycle disorders, but it remains a serious possible complication. Very high ammonia can affect consciousness and cause brain swelling. Prompt treatment is important.

Nutrition can also become complicated. Excessive protein restriction may lead to poor growth or loss of muscle, while too much protein may worsen biochemical control. Ongoing dietitian support helps balance these risks.

Follow up

Arginase deficiency requires regular, lifelong follow-up with a metabolic clinic. Routine visits usually review growth, food intake, medicines, mobility, learning, behavior, and the ability to follow the care plan.

Blood tests may monitor arginine, other amino acids, ammonia, nutrition, and liver health. The timing depends on age, treatment, recent results, and whether the person is ill. Treatment may need adjustment during growth, puberty, pregnancy, changes in activity, or transitions to adult care.

Neurologic and developmental assessments help track muscle tone, walking, seizures, communication, and school progress. Physical therapy and equipment should be reviewed as needs change. Bone and joint assessment may be appropriate for people with long-term mobility limits or contractures.

Routine follow-up should also include:

Contact the metabolic team promptly during illness, repeated vomiting, reduced food intake, or a meaningful change in alertness, movement, or behavior. These situations should not wait for the next routine appointment.

- Updating the emergency letter and sick-day instructions
- Reviewing medicines, formulas, and access to supplies

- Planning ahead for surgery, travel, or fasting procedures
- Discussing genetic counseling and family testing
- Supporting the transition from pediatric to adult metabolic care

Sources

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