CONDITION

Alkaptonuria

Learn how alkaptonuria causes dark urine, ochronosis, joint damage, and other complications, and how specialists diagnose, treat, and monitor it.

WHAT IT IS
Rare inherited amino acid breakdown disorder

BODY SYSTEM
Metabolism and connective tissues

MAIN SYMPTOMS
Dark urine, ochronosis, back and joint stiffness, urinary stones

WHAT CAUSES IT
Inherited HGD gene variants

HOW IT IS DIAGNOSED
Urine HGA measurement and genetic testing

MAIN TREATMENT
HGA-reducing and supportive treatment

CAN IT BE CURED?
No, management reduces HGA and complications

IS IT AN EMERGENCY?
Sometimes, severe breathing difficulty

LONG-TERM OUTLOOK
Complications can become significant over decades

Overview

Alkaptonuria is a rare inherited condition that affects how the body breaks down two amino acids called phenylalanine and tyrosine. Amino acids are building blocks of protein.

People with alkaptonuria cannot fully break down a substance called homogentisic acid, or HGA. HGA builds up in the body and is released in urine. When urine containing HGA is exposed to air, it may gradually turn dark brown or black.

Over many years, HGA can also collect in cartilage, tendons, heart valves, and other connective tissues. This process causes a blue-black discoloration called ochronosis . The buildup can make tissues stiff and fragile, leading to arthritis and other complications, often beginning in adulthood.

Babies with alkaptonuria are usually healthy. Dark staining in a diaper may be the first sign, but it can be missed because fresh urine may look normal. Many people are not diagnosed until they develop dark pigmentation or joint and back problems later in life.

Alkaptonuria does not usually affect intelligence or childhood development. However, its effects on joints, the spine, heart valves, and urinary system can become significant. Early recognition allows for appropriate monitoring, symptom treatment, genetic counseling, and discussion of condition-specific therapy.

Symptoms

The symptoms and their timing vary. HGA begins accumulating from birth, but many complications take decades to develop.

Possible signs and symptoms include:

Spinal and joint symptoms often begin in early or middle adulthood. The discs between the spinal bones may become hardened and narrowed. This can cause back pain, stiffness, and loss of height. Unlike some inflammatory types of arthritis, alkaptonuria-related joint disease usually results from gradual tissue damage rather than an immune-system attack.

Ochronosis may first become visible in the ears or eyes. Pigmentation in the eye usually affects the white outer area rather than vision itself. Internal pigmentation can occur in cartilage and other tissues without being visible from the outside.

Not every dark urine episode is caused by alkaptonuria. Blood, medicines, dehydration, liver problems, and other conditions can also change urine color. A laboratory test is needed to identify excess HGA.

- Urine that becomes dark brown or black after standing or exposure to air
- Dark stains in diapers, underwear, or around the toilet
- Blue, gray, or black discoloration of the whites of the eyes
- Darkening and thickening of the outer ears
- Darkened sweat or staining of clothing
- Lower back stiffness or pain
- Reduced movement of the spine
- Pain and stiffness in large joints, especially the knees, hips, and shoulders
- Tendon pain or injury

- Kidney, bladder, or prostate stones
- Heart murmur or symptoms related to a damaged heart valve

Causes and risk factors

Alkaptonuria is caused by changes, called pathogenic variants, in the HGD gene. This gene provides instructions for an enzyme that helps break down HGA. When the enzyme does not work properly, HGA accumulates.

The condition follows an autosomal recessive inheritance pattern. This means a person usually has a disease-causing HGD variant in both copies of the gene, one inherited from each biological parent.

Parents of an affected person are often carriers. Carriers have one altered copy and one working copy of the gene and generally do not develop alkaptonuria. When two carriers have a child together, each pregnancy has:

These chances apply to each pregnancy. They do not mean that exactly one out of every four children in a family will be affected.

A family history increases the likelihood of alkaptonuria. The condition may also be more common in communities where a particular HGD variant has been passed down through many generations. People whose biological parents are related may have a higher chance of inheriting two copies of the same rare recessive variant.

Lifestyle does not cause alkaptonuria. However, body weight, joint injuries, repetitive physical strain, and access to treatment may influence how symptoms affect daily life.

- A 1 in 4 chance that the child will have alkaptonuria
- A 1 in 2 chance that the child will be a carrier
- A 1 in 4 chance that the child will inherit neither familial variant

Diagnosis

Diagnosis usually begins with a medical history and examination. A clinician may ask about urine discoloration, joint symptoms, pigmentation, urinary stones, and similar findings in relatives.

The main biochemical test measures HGA in urine. A specialized laboratory technique, often called organic acid analysis, can identify and measure the excess HGA. Simply observing that

urine darkens is not enough to confirm the condition.

Genetic testing can look for disease-causing variants in both copies of the HGD gene. This may confirm the diagnosis and identify the specific familial variants. The results can also help relatives understand whether testing may be useful for them.

After diagnosis, additional tests may assess how the condition has affected the body. These depend on age, symptoms, and medical history. They may include:

A genetics professional can explain inheritance, testing options for relatives, and reproductive choices. Testing children or other relatives should be discussed with a clinician who understands genetic testing and its possible medical and emotional effects.

- X-rays or other imaging of painful joints and the spine
- An echocardiogram, which uses ultrasound to examine heart valves
- Tests for kidney or urinary stones
- Hearing, eye, or mobility assessments when symptoms suggest a problem
- Blood tests used to plan or monitor treatment

Treatment and management

Management aims to reduce HGA production when possible, preserve movement, control pain, and detect complications. Care may involve a metabolic specialist, geneticist, primary care clinician, rheumatologist, physiotherapist, dietitian, cardiologist, and orthopedic surgeon.

Nitisinone is a medicine that blocks an earlier step in the pathway that produces HGA. Clinical trials have shown that it can sharply reduce HGA levels and slow some signs of disease progression. It is authorized for the treatment of adults with alkaptonuria in some regions, including the European Union. Availability and approved uses differ by country.

Nitisinone raises the level of tyrosine in the blood. High tyrosine can cause eye problems and may have other effects. People taking it need specialist monitoring, including blood tests. New eye pain, redness, light sensitivity, or changes in vision should be reported promptly. Treatment decisions should account for the person's age, disease effects, local approvals, and ability to complete monitoring.

A dietitian may recommend adjusting protein intake, particularly during nitisinone treatment, because protein contains phenylalanine and tyrosine. A severely restricted diet can cause nutritional problems and should not be started without professional guidance. Evidence that dietary restriction alone prevents long-term complications is limited.

Exercise helps maintain strength, balance, and joint movement. Lower-impact activities such as swimming, cycling, and controlled strengthening may be easier on affected joints. A physiotherapist can adapt activity to pain, stiffness, previous injuries, and mobility needs. Long periods of inactivity can worsen weakness and reduce function.

Pain management is individualized. It may involve heat or cold, activity changes, physiotherapy, and nonprescription or prescription pain medicines. Medicines have different risks depending on kidney health, heart disease, stomach problems, and other factors, so a clinician or pharmacist should help select appropriate options.

Joint replacement may be considered when severe hip, knee, or shoulder damage causes persistent pain and loss of function. Surgery can also be used for certain tendon injuries, urinary stones, or seriously damaged heart valves. Alkaptonuria does not automatically rule out surgery, but the surgical team should know about the diagnosis because affected tissues may be unusually pigmented or fragile.

High-dose vitamin C has been studied, but it has not been shown to prevent the major complications of alkaptonuria. Supplements should be discussed with a clinician because high doses can cause adverse effects and may not provide benefit.

Complications

Long-term HGA accumulation can cause ochronotic arthropathy , meaning joint disease related to ochronosis. Spinal discs may calcify and narrow, while large joints can develop severe wear. This may limit walking, work, sleep, and other activities.

Tendons and ligaments can become stiff or fragile. Injuries may occur with less force than expected, including rupture of the Achilles tendon at the back of the ankle.

HGA-related material can contribute to stones in the kidneys, bladder, or prostate. Stones may cause pain, blood in the urine, infection, or difficulty passing urine.

Deposits may also occur in heart valves, especially the aortic or mitral valve. A valve can become narrowed or may not close properly. Some people need monitoring by a cardiologist, and severe valve disease may eventually require treatment.

Seek urgent medical advice for severe flank pain, fever with urinary symptoms, inability to pass urine, a suddenly swollen painful joint, or a suspected tendon rupture. Call emergency services for chest pressure, severe breathing difficulty, fainting, or sudden weakness or speech difficulty. These symptoms can have many causes and require prompt assessment rather than being assumed to result from alkaptonuria.

Follow up

Routine follow-up should be coordinated with a clinician familiar with metabolic disorders. The schedule depends on age, symptoms, current treatment, and previous test results.

Visits may review pain, mobility, exercise, work or school needs, urinary symptoms, and changes in hearing, vision, or pigmentation. Clinicians may examine the spine and joints and assess whether physiotherapy, mobility aids, or pain-management changes would help.

Heart evaluation becomes increasingly important in adulthood. A clinician may listen for a heart murmur and decide when an echocardiogram or cardiology review is appropriate. Kidney and urinary evaluation may be needed if there is a history of stones, infections, blood in the urine, or difficulty urinating.

People taking nitisinone need regular monitoring of HGA, tyrosine, nutrition, and possible medicine-related effects. Follow-up should not be stopped simply because pain or urine discoloration improves.

Relatives may wish to discuss carrier testing or diagnostic testing after the familial HGD variants are known. Genetic counseling can help families understand what results may mean before testing is arranged.

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