CONDITION

Urea cycle disorders

Urea cycle disorders are inherited conditions that allow toxic ammonia to build up in the blood.

WHAT IT IS
Inherited conditions that impair the body's removal of nitrogen

BODY SYSTEM
Liver, brain, and nervous system

MAIN SYMPTOMS
Vomiting, poor feeding, unusual sleepiness, confusion

WHAT CAUSES IT
Inherited changes affecting urea-cycle enzymes or transporters

HOW IT IS DIAGNOSED
Blood ammonia, amino acids, urine tests, genetic testing

MAIN TREATMENT
Dietary planning, nitrogen-removing medicines, emergency ammonia control

CAN IT BE CURED?
Sometimes - liver transplant corrects ammonia processing

IS IT AN EMERGENCY?
Sometimes - confusion, severe sleepiness, or seizures

LONG-TERM OUTLOOK
Early control helps, but crises may cause lasting harm

Overview

Urea cycle disorders are a group of rare, inherited metabolic conditions. "Metabolic" means they affect how the body processes nutrients and waste products.

When your body breaks down protein, it produces nitrogen. The liver normally changes this nitrogen into urea through a series of chemical steps called the urea cycle. Urea then leaves the body in urine.

In a urea cycle disorder, one of the enzymes or transport proteins needed for this process does not work properly. Nitrogen can then collect in the blood as ammonia. A high ammonia level is called hyperammonaemia .

Ammonia is especially harmful to the brain. A large or rapid increase can affect alertness,

behaviour, movement, and breathing. Without prompt treatment, it can cause brain swelling and lasting injury.

Some urea cycle disorders cause severe symptoms within the first days of life. Others leave part of the cycle working and may not become apparent until childhood or adulthood. Symptoms may first appear during an illness, after prolonged fasting, following surgery, or during another period when the body is breaking down more protein than usual.

The group includes ornithine transcarbamylase deficiency, citrullinaemia type 1, argininosuccinic aciduria, arginase 1 deficiency, carbamoyl phosphate synthetase 1 deficiency, and N-acetylglutamate synthase deficiency. Their symptoms overlap, but treatment details differ.

Symptoms

Symptoms depend on how much urea-cycle function remains and how high the ammonia level becomes. They can develop quickly and may resemble infection, stomach illness, migraine, intoxication, or a mental health problem.

In a newborn, possible symptoms include:

People with a partial disorder may have episodes rather than constant symptoms. Possible features include repeated vomiting, headaches, confusion, unusual tiredness, poor coordination, or sudden changes in behaviour. Some people become unusually agitated or appear intoxicated.

Children may have difficulties with growth, learning, attention, planning, or coordination. They may naturally avoid high-protein foods because eating them makes them feel unwell. However, food preferences alone do not show that someone has a urea cycle disorder.

Arginase 1 deficiency can have a different course. It often causes increasing muscle stiffness, walking difficulties, or developmental concerns rather than sudden severe ammonia crises, although high ammonia can still occur.

Illness, dehydration, fasting, surgery, childbirth, and some medicines can trigger symptoms in a person whose condition was previously mild or unrecognised.

- Poor feeding, vomiting, or difficulty coordinating feeds
- Unusual sleepiness, irritability, or weak muscle tone
- Rapid breathing or changes in body temperature
- Seizures, reduced responsiveness, or coma

Causes and risk factors

Urea cycle disorders are caused by changes in genes that provide instructions for urea-cycle enzymes or transport proteins.

Most are inherited in an autosomal recessive pattern. This means a child usually inherits one altered gene copy from each parent. The parents are generally healthy carriers.

Ornithine transcarbamylase deficiency is usually X-linked , meaning the affected gene is on the X chromosome. It can affect people of any sex. People with two X chromosomes may have mild, severe, or no obvious symptoms because the amount of working enzyme can differ between cells.

Occasionally, a gene change occurs for the first time in a child rather than being inherited from a parent. A family may therefore have no known history of the condition.

The gene change determines the underlying disorder, but it does not always predict how severe it will be. People in the same family can have different symptoms.

Factors that can increase the chance of an ammonia crisis include:

These factors do not cause the inherited condition. They can reveal it or worsen an existing problem.

- Fever, infection, vomiting, or diarrhoea
- Going without food for an extended period
- Major injury, surgery, or other physical stress
- Pregnancy and especially the period after childbirth
- Sudden major changes in protein intake
- Certain medicines, including valproate, in susceptible people

Diagnosis

A blood ammonia test is central to diagnosis. Because ammonia levels can change quickly, the blood sample must be collected, handled, and analysed correctly. An unexpectedly high result may need urgent confirmation, but treatment should not be delayed when symptoms and results indicate a serious rise.

Further blood tests measure amino acids, which are the building blocks of protein. A urine test may measure orotic acid and other substances. The pattern of these results helps identify which part of the urea cycle is affected.

Genetic testing can confirm many urea cycle disorders and identify the specific gene change. In uncommon situations, further biochemical or enzyme testing may be needed.

Doctors may also check blood sugar, liver function, kidney function, blood gases, and signs of infection. These tests help assess the effects of high ammonia and rule out other causes.

Some urea cycle disorders may be found through newborn screening, but screening programmes differ by location. Newborn screening does not reliably detect every disorder or every mildly affected baby. A normal newborn screening result therefore does not exclude all urea cycle disorders.

After a diagnosis, close relatives may be offered genetic testing or biochemical tests. Genetic counselling can help a family understand inheritance and testing options.

Treatment and management

A sudden rise in ammonia requires hospital treatment. The immediate goals are to stop ammonia production, provide enough energy to prevent the body from breaking down its own tissues, and remove ammonia from the blood.

Treatment may include intravenous glucose and fats, medicines that carry nitrogen out of the body through alternative pathways, and carefully selected amino acid supplements. Protein may be paused briefly during an acute crisis, but prolonged protein restriction can be harmful.

When ammonia is very high or is not falling quickly enough, dialysis may be used. Dialysis filters waste from the blood and can remove ammonia faster than medicines alone.

Long-term treatment is tailored to the specific disorder, age, growth needs, symptoms, and test results. It may include:

N-acetylglutamate synthase deficiency may respond to a medicine that replaces the missing chemical signal needed to start the urea cycle. This treatment is specific to certain causes of high ammonia.

A liver transplant can provide enough working urea-cycle activity to prevent future metabolic crises. It may be considered when control is difficult or crises are severe. Transplantation has major risks and requires lifelong anti-rejection medicine. It also cannot reverse brain injury that happened before surgery.

People with a diagnosed disorder usually receive a written emergency plan. It explains what should happen during illness, fasting, surgery, or pregnancy and should be available to emergency teams.

Medicines commonly used for this include phenylbutyrate . Which one suits you, if any, is a

decision for you and your doctor.

- A planned amount of dietary protein that supports growth without excessive nitrogen
- Special medical formulas or essential amino acid mixtures
- Nitrogen-removing medicines, sometimes called ammonia scavengers
- Arginine or citrulline supplements for selected disorders
- Regular blood tests and reviews with a metabolic dietitian

Complications

The main concern is injury to the brain from high ammonia. A severe episode can cause seizures, brain swelling, coma, or death. Even shorter episodes may affect memory, attention, learning, coordination, or behaviour.

The risk of lasting effects is influenced by how high ammonia rises, how long it remains high, and how often crises occur. A person can still have thinking or learning difficulties between episodes even when routine ammonia results are acceptable.

Other possible complications include poor growth, nutritional deficiencies, low bone density, movement problems, and liver abnormalities. Argininosuccinic aciduria can also affect the liver and hair. Arginase 1 deficiency may cause progressive stiffness and weakness in the legs.

Treatment itself needs monitoring. A diet that is too restrictive may not provide enough protein, calories, vitamins, or minerals. Nitrogen-removing medicines can also cause side effects. This is why dietary changes should be guided by a specialist metabolic team.

Prevention

The inherited gene change that causes a urea cycle disorder cannot usually be prevented.

Genetic counselling can explain the chance of passing the condition on. If the family's gene change is known, options may include testing during pregnancy or testing embryos created through in vitro fertilisation. These are personal choices, not requirements.

Ammonia crises cannot always be prevented, but their risk may be reduced through regular treatment and early action during illness. A person with a diagnosed disorder should follow their individual sick-day and emergency plan, avoid prolonged fasting, and tell the metabolic team before planned surgery or pregnancy.

A medical alert bracelet, emergency letter, or phone record can help unfamiliar healthcare

teams recognise the condition quickly.

Living with it and what to expect

The course of a urea cycle disorder differs widely. Some people need daily dietary and medical treatment from infancy. Others have partial enzyme activity and remain well for long periods but still face a risk of crisis during physical stress.

Routine care usually involves a metabolic specialist, dietitian, and primary care clinician. Follow-up may include blood tests, nutrition checks, growth monitoring, and assessment of learning or movement. Children may benefit from school support or developmental services.

Meals and medicines can require planning, especially around travel, school, exercise, and social events. The goal is not to remove all protein. Protein is essential for muscles, organs, healing, and growth, so intake must be balanced carefully.

Teenagers and young adults need a planned move from children's to adult metabolic services. Learning the medicine schedule, emergency plan, and early warning symptoms can support greater independence.

Pregnancy requires specialist planning because nutritional needs change. The period during and after childbirth can increase protein breakdown and the risk of high ammonia, including in people who previously had few symptoms.

With early diagnosis and consistent management, many people attend school, work, travel, and take part in family life. However, the risk of future episodes does not always disappear, and some people need lifelong support for neurological or developmental effects.

When to get medical help

If you or someone you care for has a urea cycle disorder, follow the personal emergency plan during illness. Contact the metabolic team promptly for fever, repeated vomiting, diarrhoea, poor food intake, or difficulty taking prescribed treatment. Early advice may prevent a crisis from becoming severe.

Seek emergency medical care for:

Tell emergency staff about the urea cycle disorder and show them the emergency letter. Do not wait for symptoms to resolve on their own or try to manage severe symptoms by making major dietary changes at home.

Arrange routine follow-up for concerns such as poor growth, recurring headaches, medicine

side effects, increasing muscle stiffness, school difficulties, or trouble following the nutrition plan. Pregnancy and planned surgery should also be discussed with the metabolic team in advance.

- Sudden confusion, extreme agitation, or unusual behaviour
- Increasing sleepiness or difficulty waking
- Repeated vomiting with weakness or reduced alertness
- New problems with balance, speech, or coordination
- A seizure, collapse, or loss of consciousness
- Abnormal breathing or rapidly worsening symptoms

Common questions

Are urea cycle disorders always found in babies?

No. Severe forms often appear in the first days of life, but partial disorders may first cause symptoms in childhood or adulthood. An illness, surgery, prolonged fasting, or childbirth may trigger the first recognised episode.

Can I have a urea cycle disorder if my newborn screening was normal?

Yes. Newborn screening differs between regions and does not detect every urea cycle disorder. Mild or partial forms may also be missed. Symptoms and diagnostic blood, urine, and genetic tests remain important.

Can someone with a urea cycle disorder eat protein?

Usually, yes. The body needs protein, but the amount and sources may need careful planning. Excessive restriction can cause poor growth and muscle breakdown, which may increase ammonia production. A metabolic dietitian should guide the plan.

Does high ammonia always cause obvious symptoms?

Not always. A modest rise may cause vague symptoms such as headache, vomiting, irritability, or difficulty concentrating. A rapid or large rise can cause severe neurological symptoms. Blood testing is needed to know the ammonia level.

Can a liver transplant cure a urea cycle disorder?

A successful liver transplant can correct the liver's inability to process nitrogen and prevent further ammonia crises. It does not repair earlier brain injury, and it brings surgical risks and lifelong anti-rejection treatment.

Can adults suddenly develop a urea cycle disorder?

The inherited condition is present from birth, but symptoms can first appear in adulthood. This is more likely when part of the urea cycle still works and a major physical stress causes ammonia to rise.

Sources

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