CONDITION

Hyperammonemia due to ornithine transcarbamylase deficiency

An inherited metabolic condition in which the body cannot safely remove ammonia from broken-down protein.

WHAT IT IS
Inherited urea-cycle condition causing harmful ammonia buildup

BODY SYSTEM
Liver metabolism and nervous system

MAIN SYMPTOMS
Vomiting, unusual sleepiness, confusion, seizures

WHAT CAUSES IT
Inherited OTC gene change reducing enzyme activity

HOW IT IS DIAGNOSED
Ammonia, amino acid, urine orotate, and genetic testing

MAIN TREATMENT
Protein management, nitrogen-scavenging medicines, emergency ammonia removal

CAN IT BE CURED?
Sometimes - liver transplant restores ammonia control

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

LONG-TERM OUTLOOK
Good control is possible; crises may cause lasting brain injury

Overview

Hyperammonemia means there is too much ammonia in the blood. Ammonia forms when the body breaks down protein. It is normally converted into urea in the liver and removed in urine.

Ornithine transcarbamylase, or OTC, is one of the enzymes needed for this process. When OTC activity is too low, the urea cycle cannot clear ammonia properly. Ammonia can then rise quickly, especially during illness, fasting, or other physical stress.

High ammonia affects the brain. A sudden rise, called a hyperammonemic crisis, may cause vomiting, confusion, extreme sleepiness, seizures, or loss of consciousness. This requires urgent treatment.

OTC deficiency is inherited, but its effects differ widely. Some babies become critically unwell soon after birth. Other people have partial enzyme activity and may not develop clear symptoms until childhood or adulthood.

Symptoms

Symptoms depend on how much OTC activity remains and how high the ammonia level becomes. They may come and go rather than being present every day.

A newborn with severe OTC deficiency may initially appear well, then develop poor feeding, vomiting, rapid breathing, unusual sleepiness, low muscle tone, or difficulty maintaining body temperature. Without treatment, seizures or coma can occur.

Children and adults with partial deficiency may have less obvious episodes. Possible symptoms include:

Some people naturally avoid high-protein foods because eating them makes them feel unwell. Others have learning, attention, mood, or movement difficulties related to earlier ammonia exposure.

Symptoms may appear during an infection, after prolonged fasting, following surgery or childbirth, or during another period when the body is breaking down its own tissues.

- Repeated vomiting or severe nausea
- Headache, confusion, poor coordination, or slurred speech
- Unusual sleepiness, agitation, or changes in behaviour
- Trouble concentrating or a decline in school or work performance
- Seizures or loss of consciousness during a severe episode

Causes and risk factors

OTC deficiency is caused by a harmful change in the OTC gene. This gene provides instructions for making the ornithine transcarbamylase enzyme.

The condition is X-linked, meaning the gene is on the X chromosome. Males usually have one X chromosome, so a harmful change can leave them with little or no working OTC enzyme. Females usually have two X chromosomes, but they can still develop symptoms because cells do not use both X chromosomes equally.

A person with an OTC gene change may inherit it from a parent. It can also result from a new

genetic change, with no previous family history.

The main risk for a crisis is increased protein breakdown inside the body. Triggers can include:

The condition itself is present from birth, even when symptoms first appear much later.

- Fever, infection, vomiting, or poor food intake
- Fasting or a sudden restrictive diet
- Surgery, injury, or another major physical stress
- Pregnancy and especially the period after childbirth
- A sudden large protein intake
- Certain medicines that affect ammonia metabolism

Diagnosis

A blood ammonia test is central to diagnosis. Because sample handling affects the result, the blood must be collected and processed correctly. A high result is usually repeated promptly while treatment decisions are being made.

Other blood tests measure amino acids, including citrulline and glutamine. A urine test measures orotic acid, a substance that is often increased in OTC deficiency. Liver function, blood sugar, blood gases, kidney function, and infection tests may help identify a trigger or rule out other causes.

Genetic testing can confirm a harmful change in the OTC gene. If genetic testing is inconclusive but suspicion remains strong, specialist testing of OTC enzyme activity in liver tissue may sometimes be considered.

Newborn screening does not reliably identify every person with OTC deficiency. A normal newborn screening result therefore does not completely exclude the condition.

Testing during a suspected crisis should not delay ammonia-lowering treatment. Close relatives may also be offered genetic testing when a familial gene change is known.

Treatment and management

A hyperammonemic crisis is treated in hospital. The immediate goals are to stop ammonia production, provide enough energy to reduce the breakdown of body tissues, and remove ammonia from the blood.

Protein may be stopped briefly under specialist supervision while calories are provided, often

through glucose and sometimes fat given into a vein. Protein must then be restarted carefully because the body still needs it for growth, tissue repair, and health.

Nitrogen-scavenging medicines help remove nitrogen through pathways that do not rely on the urea cycle. Arginine or citrulline may also be used to support the parts of the cycle that still work. If ammonia is very high, rising quickly, or causing severe neurological symptoms, dialysis may be needed to remove it rapidly.

Long-term management is coordinated by a specialist metabolic team. It may include:

Protein should not be severely restricted without specialist guidance. Too little can cause poor growth, muscle loss, and nutritional deficiencies.

Liver transplantation can provide enough working OTC enzyme to prevent further hyperammonemic crises. It requires major surgery and lifelong follow-up, including medicines that suppress the immune system. It does not remove the inherited gene change from the rest of the body or reverse brain injury that has already occurred.

- A protein intake tailored to age, growth, and remaining enzyme activity
- Enough calories to prevent the body from breaking down its own tissues
- Nitrogen-scavenging medicine
- Citrulline or arginine supplements when appropriate
- Regular blood tests and nutrition reviews
- A written emergency plan for illness, fasting, surgery, or vomiting

Complications

The main complication is injury to the brain from high ammonia. A severe or prolonged crisis can cause brain swelling, seizures, coma, or death. Earlier treatment generally gives a better chance of limiting injury, but outcomes cannot be predicted from one ammonia result alone.

Repeated episodes may affect memory, attention, planning, learning, mood, or movement. Some people need educational support even when ammonia is usually controlled.

Poorly balanced protein restriction can cause inadequate growth or nutrient deficiencies. Liver transplantation avoids future ammonia crises but introduces separate risks related to surgery, rejection, infection, and immune-suppressing treatment.

Prevention

OTC deficiency cannot currently be prevented because it is caused by an inherited gene change. However, many hyperammonemic episodes can be avoided or treated earlier.

A personal emergency plan should explain what to do during fever, vomiting, reduced food intake, surgery, or another physical stress. People with OTC deficiency are often advised to carry medical identification and a copy of this plan.

Medicines, supplements, fasting plans, and major dietary changes should be reviewed with the metabolic team. Planned surgery and pregnancy need advance coordination because both can increase the risk of a crisis.

Genetic counselling can explain inheritance and testing options. If the familial OTC change is known, prenatal testing or testing of embryos during in vitro fertilisation may be possible. These choices are personal and do not prevent the gene change from arising in a family for the first time.

Living with it and what to expect

The course ranges from severe illness in early infancy to occasional episodes beginning in adulthood. Remaining OTC activity, past ammonia exposure, access to treatment, and future physical stresses all influence what happens over time.

Between episodes, many people feel well and take part in school, work, exercise, and family life. Daily management may still involve medicine, planned meals, laboratory monitoring, and carrying emergency information. Children need regular reviews of growth, nutrition, learning, and development.

A crisis can occur after a long stable period. Illness plans remain important even when ammonia levels have been controlled for years. Family members, schools, and workplaces may need to know how to recognise symptoms without unnecessarily limiting normal activities.

Women with an OTC gene change need specialist planning for pregnancy and the weeks after delivery. Adults moving from children's services also benefit from a planned transfer to an adult metabolic team.

When to get medical help

Call emergency services or go to an emergency department if you or someone with possible or confirmed OTC deficiency has:

If an emergency letter or illness plan is available, take it with you. Tell the emergency team

about OTC deficiency or the possibility of hyperammonemia. Do not wait for symptoms to improve on their own.

Contact the metabolic team promptly for fever, vomiting, reduced eating, or difficulty taking prescribed treatment. This is especially important for infants, during pregnancy, after childbirth, or before surgery.

Routine follow-up is used to review growth, nutrition, medicines, blood results, learning, and emotional wellbeing. New mild symptoms or problems following the management plan can usually be discussed at these visits or through the specialist team's usual contact route.

- New confusion, severe agitation, or unusual behaviour
- Marked sleepiness or difficulty being awakened
- A seizure, collapse, or loss of consciousness
- Repeated vomiting together with weakness or drowsiness
- Poor coordination, slurred speech, or rapidly worsening symptoms

Common questions

Can OTC deficiency first appear in an adult?

Yes. The gene change is present from birth, but someone with partial enzyme activity may remain well until illness, surgery, childbirth, fasting, or another stress causes ammonia to rise.

Can women have OTC deficiency symptoms?

Yes. Women and girls can have mild, intermittent, or severe symptoms. This happens because the two X chromosomes are not equally active in every cell. A woman without previous symptoms may still be at risk during major physical stress.

Can I eat protein if I have OTC deficiency?

Protein is essential, so it is not usually removed completely. The amount and type need to be tailored by a metabolic dietitian. Severe self-imposed restriction can cause malnutrition and may increase the breakdown of body tissues.

Does liver transplantation cure OTC deficiency?

A successful transplant can correct the liver's inability to run the urea cycle and prevent future ammonia crises. It does not change the inherited variant elsewhere in the body or repair existing brain injury.

Is high ammonia always caused by OTC deficiency?

No. High ammonia can result from other urea-cycle conditions, severe liver disease, certain

medicines, infections, and several rare metabolic problems. Blood, urine, and genetic tests help identify the cause.

Can OTC deficiency be passed to children?

Yes. It follows an X-linked inheritance pattern. The chance for each child depends on which parent carries the gene change and the child's chromosomes. Genetic counselling can explain the possibilities for a particular family.

Sources

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