CONDITION

Hereditary nonspherocytic hemolytic anemia

An inherited condition in which red blood cells break down too early because of an enzyme or related cell defect.

WHAT IT IS
Inherited breakdown of red blood cells without typical spherical cells

BODY SYSTEM
Blood and circulation

MAIN SYMPTOMS
Fatigue, jaundice, pale skin, dark urine

WHAT CAUSES IT
Inherited red blood cell enzyme defects

HOW IT IS DIAGNOSED
Red cell enzyme assays and genetic testing

MAIN TREATMENT
Supportive care, transfusions, and cause-specific treatment

CAN IT BE CURED?
Sometimes - stem cell transplant cures selected severe cases

IS IT AN EMERGENCY?
Sometimes - severe breathlessness, fainting, or rapidly worsening weakness

LONG-TERM OUTLOOK
Often manageable, from mild to transfusion-dependent illness

Overview

Hereditary nonspherocytic hemolytic anemia, or HNHA, is a group of inherited conditions in which red blood cells break down earlier than normal. This breakdown is called hemolysis . If the body cannot replace the cells quickly enough, anemia develops.

"Nonspherocytic" means that the blood cells do not usually have the round, sphere-like appearance seen in hereditary spherocytosis. The name is descriptive rather than a single exact diagnosis. Finding the underlying subtype matters because treatment, triggers, inheritance, and long-term risks can differ.

HNHA is often caused by a problem with an enzyme that red blood cells need to produce energy or protect themselves from damage. Pyruvate kinase deficiency and glucose-6-phosphate dehydrogenase deficiency, or G6PD deficiency, are important examples.

Several much rarer enzyme defects can produce a similar pattern.

Some people have mild, stable anemia. Others experience ongoing jaundice, sudden episodes of hemolysis, or a need for regular blood transfusions.

Symptoms

Symptoms reflect anemia and the release of material from broken-down red blood cells. They may begin in infancy, childhood, or adulthood.

Possible symptoms include:

Newborns with some forms can develop significant jaundice. A person with a mild form may have few symptoms until an infection or another trigger increases red blood cell breakdown.

Symptoms are not identical across subtypes. Pyruvate kinase deficiency commonly causes ongoing hemolysis. G6PD deficiency more often causes sudden episodes after certain infections, medicines, chemicals, or foods, although some forms cause chronic anemia.

- Tiredness, weakness, or reduced exercise tolerance
- Pale skin, shortness of breath, or a fast heartbeat
- Yellowing of the skin or eyes, called jaundice
- Dark brown or tea-colored urine during increased hemolysis
- An enlarged spleen, which may cause fullness under the left ribs
- Gallstones, sometimes causing upper abdominal pain

Causes and risk factors

HNHA is caused by a change in a gene involved in red blood cell function. Many forms affect enzymes that help cells make energy or handle oxidative stress , which is chemical stress that can damage the cell.

Pyruvate kinase deficiency and many other red cell enzyme conditions usually follow an autosomal recessive inheritance pattern. This generally means a person inherits one altered copy of the gene from each parent. The parents are often healthy carriers.

G6PD deficiency is linked to the X chromosome. It is more likely to cause clear symptoms in males, but females can also have low enzyme activity and clinically important hemolysis.

A family history increases the chance of an inherited condition, but its absence does not rule one out. Parents may not know they are carriers, and mild cases may never have been

identified.

Factors that can worsen hemolysis include infections and, in some subtypes, certain medicines or chemicals. Fava beans can trigger hemolysis in some people with G6PD deficiency. These are not universal HNHA triggers, so advice should be based on the confirmed enzyme defect.

Diagnosis

Diagnosis starts with blood tests that look for anemia and increased red blood cell breakdown. These may include a complete blood count, a reticulocyte count, bilirubin, lactate dehydrogenase, and haptoglobin. Reticulocytes are young red blood cells released when bone marrow is trying to replace lost cells.

A blood smear allows the cells to be examined under a microscope. HNHA does not usually produce the large number of spherical cells expected in hereditary spherocytosis. However, cell appearance alone cannot confirm a particular enzyme defect.

A direct antiglobulin test, also called a Coombs test, may be used to help exclude immune hemolytic anemia. Tests for hemoglobin or red cell membrane conditions may be needed when the cause remains uncertain.

Confirming HNHA usually requires measuring specific enzyme activity in red blood cells and identifying a relevant gene change. Recent transfusions can interfere with enzyme tests because donated cells may have normal activity. A high number of young red cells can also make some enzyme results appear more normal than they are. Testing may therefore need careful timing, genetic confirmation, or repetition.

Once a subtype is identified, relatives may be offered targeted testing if they want to understand their own risk.

Treatment and management

Treatment is based on the exact cause, the severity of anemia, symptoms, and complications. Mild cases may need monitoring rather than regular treatment.

Folic acid may be recommended because the bone marrow uses more folate while producing extra red blood cells. Iron supplements are not routine treatment for hemolytic anemia. They should generally be used only when testing confirms iron deficiency, because some forms of HNHA can cause iron overload.

Blood transfusions can treat severe or symptomatic anemia. Some people need them only

during an infection, pregnancy, surgery, or sudden hemolytic episode. Others with severe forms need scheduled transfusions.

Iron can build up after repeated transfusions. It may also accumulate in some chronically hemolytic conditions without frequent transfusions. If testing shows harmful iron overload, treatment may include medicines that remove iron from the body, called chelation therapy.

Removing the spleen, known as splenectomy, can improve anemia and reduce transfusion needs in selected people, particularly with pyruvate kinase deficiency. It does not correct the genetic defect or completely stop hemolysis. Splenectomy creates lifelong risks of serious infection and blood clots, so vaccination, infection precautions, and preventive medicines may be needed.

Mitapivat is an oral medicine that activates pyruvate kinase. It can improve anemia in some eligible adults with pyruvate kinase deficiency. It does not treat other forms of HNHA, and response can be affected by the particular gene changes present.

A stem cell transplant can replace the blood-forming system and may cure selected severe cases. Because transplantation can cause major complications, it is generally considered only when the expected benefit outweighs those risks.

Gallstones or other complications are treated separately. During a G6PD-related episode, management usually involves removing the trigger, treating an infection if present, and providing supportive care or a transfusion when needed.

Complications

Long-term hemolysis can lead to bilirubin gallstones, an enlarged spleen, and iron overload. Excess iron can damage the liver, heart, hormone-producing organs, and other tissues if it becomes severe.

An infection with parvovirus B19 can briefly stop red blood cell production. In someone whose cells already have a short lifespan, this can cause a rapid fall in hemoglobin, known as an aplastic crisis.

Less common complications include bone changes, leg ulcers, high pressure in the lung circulation, or blood clots. Clotting risk can be higher after splenectomy.

Not everyone develops these problems. Regular monitoring is intended to identify them before they cause lasting harm.

Prevention

The inherited gene change that causes HNHA cannot be prevented through diet, exercise, or lifestyle choices.

Some hemolytic episodes and complications can be prevented. This may include avoiding confirmed triggers, treating infections promptly, and checking medicines with a pharmacist or medical professional familiar with the specific subtype. A general internet list of "unsafe" medicines is not a substitute for advice based on the diagnosed enzyme defect.

Monitoring for iron overload and gallstones can reduce the chance that complications go unnoticed. People without a spleen need a specific vaccination and infection-safety plan.

Genetic counselling can explain inheritance and the chance of passing the condition to a child. When the gene change is known, carrier, pregnancy, or embryo testing may be available for those who want it.

Living with it and what to expect

HNHA is lifelong unless successfully treated with a stem cell transplant. Its course can range from mild anemia with occasional check-ups to severe anemia requiring ongoing treatment.

A person's usual hemoglobin level may remain fairly stable for long periods. Infections, pregnancy, surgery, or subtype-specific triggers can temporarily worsen hemolysis. Over years, attention may shift toward iron levels, gallstones, spleen-related issues, and the effects of chronic anemia.

Routine follow-up may include blood counts, markers of hemolysis, and iron testing. Some people need scans to measure iron in the liver or heart. Follow-up after splenectomy also includes infection and clotting precautions.

Many people can study, work, exercise, travel, and have families. Activities may need to be adjusted during periods of anemia. Pregnancy is possible, but planning ahead allows anemia, transfusion needs, medicines, and inheritance to be reviewed.

The outlook is generally better when the subtype is identified and complications are monitored. Severe forms can have a greater effect on daily life and long-term health, particularly when anemia or iron overload is difficult to control.

When to get medical help

Seek emergency care for:

Contact your medical team promptly for a sudden increase in jaundice, dark urine, breathlessness, or fatigue. These changes may indicate increased hemolysis or a significant drop in hemoglobin.

Fever or shaking chills after splenectomy require immediate medical advice because serious infections can progress quickly. Follow the emergency plan provided after surgery.

A newborn with jaundice, poor feeding, unusual sleepiness, or worsening yellow coloration needs urgent assessment. Newborn jaundice has several possible causes and should not be attributed to HNHA without testing.

Routine follow-up is the right setting for gradually changing fatigue, recurring abdominal discomfort, medication checks, family testing, and discussion of pregnancy or travel plans.

- Severe difficulty breathing, chest pain, fainting, confusion, or difficulty waking
- Rapidly worsening weakness with marked paleness or a pounding heartbeat
- Signs of a serious reaction during or soon after a blood transfusion
- Severe illness or collapse, especially in someone without a spleen

Common questions

Is HNHA the same as hereditary spherocytosis?

No. Both are inherited causes of hemolytic anemia, but hereditary spherocytosis usually results from a problem with the red cell membrane and produces characteristic spherical cells. HNHA is more often linked to enzyme defects and lacks that typical pattern.

Can hereditary nonspherocytic hemolytic anemia be cured?

Most treatments control anemia and complications rather than remove the cause. A stem cell transplant may cure selected severe cases, but its risks make it unsuitable for many people. Mitapivat can improve some cases of pyruvate kinase deficiency but is not considered a cure.

Will I need blood transfusions for life?

Not necessarily. Some people never need a transfusion, while others need one only during an illness or another period of increased stress. Severe forms may require regular transfusions. The confirmed subtype and your usual hemoglobin level help clarify what is likely.

What foods or medicines should I avoid?

There is no single avoidance list for every form of HNHA. Fava beans and certain medicines are important triggers for some people with G6PD deficiency, but they are not universal triggers. Use a list provided for your specific diagnosis and check unfamiliar medicines before taking

them.

Can I pass HNHA to my children?

Yes, but the chance depends on the gene involved and whether the other biological parent carries a relevant change. Many forms are autosomal recessive, while G6PD deficiency is X-linked. Genetic counselling can provide a more specific estimate.

Does dark urine mean my kidneys are failing?

Not usually. During hemolysis, dark urine may come from hemoglobin released by broken red blood cells. However, dark urine can have other causes, and severe hemolysis can affect kidney function. A sudden change should be assessed promptly, especially if urine output falls or you feel unwell.

Sources

- Bianchi P, Fermo E, Glader B, and colleagues. "Addressing the diagnostic gaps in pyruvate kinase deficiency: Consensus recommendations on the diagnosis of pyruvate kinase deficiency." American Journal of Hematology . 2019;94(1):149-161.
- Grace RF, Bianchi P, van Beers EJ, and colleagues. "The clinical spectrum of pyruvate kinase deficiency: Data from the Pyruvate Kinase Deficiency Natural History Study." Blood . 2018;131(20):2183-2192.
- Koralkova P, van Solinge WW, van Wijk R. "Rare hereditary red blood cell enzymopathies associated with hemolytic anemia: Pathophysiology, clinical aspects, and laboratory diagnosis." International Journal of Laboratory Hematology . 2014;36(3):388-397.
- Luzzatto L, Ally M, Notaro R. "Glucose-6-phosphate dehydrogenase deficiency." Blood . 2020;136(11):1225-1240.
- Al-Samkari H, Galactéros F, Glenthøj A, and colleagues. "Mitapivat versus placebo for pyruvate kinase deficiency." New England Journal of Medicine . 2022;386:1432-1442.
- U.S. Food and Drug Administration. PYRUKYND (mitapivat) prescribing information . Agios Pharmaceuticals.