Dehydrated hereditary stomatocytosis (DHS):information for patients

What is dehydrated hereditary stomatocytosis?

Dehydrated hereditary stomatocytosis (DHS), sometimes called hereditary xerocytosis, is a rare inherited condition affecting the red blood cells.

A red blood cell is essentially a bag of haemoglobin that has to stay soft enough to squeeze through blood vessels narrower than itself. Keeping it soft depends on getting the water content right, and the water content depends on the salts inside the cell. In DHS, one of the gates in the cell wall does not close properly. Potassium leaks out, water follows it, and the cell is left dry, dense and stiff.

A stiff red blood cell does not survive long. The spleen, whose job is to pull damaged cells out of circulation, removes them earlier than it should. This early breakdown is called haemolysis, and it is what causes the anaemia, the jaundice and the gallstones that come with this condition.

The name comes from what some of the cells look like down a microscope: a slit-shaped pale area across the middle, like a mouth, or stoma. It is a name based on an appearance rather than on the actual problem, which is part of why the condition is so often misidentified.

DHS is a condition of water and salt balance in the red blood cell, not a shortage of anything. This matters more than it sounds, because the treatment that helps most other haemolytic anaemias — removing the spleen — is harmful in DHS.

What causes it?

Two genes account for most cases, and both of them make gates that sit in the wall of the red blood cell.

PIEZO1 is the commonest. It makes a channel that opens when the cell is squeezed — the cell's way of sensing pressure as it is pushed through small vessels. In DHS the channel is slow to close after it opens, so every squeeze leaks a little more salt and water than it should.

KCNN4, also known as the Gardos channel, accounts for most of the rest. It is a potassium gate, and the changes seen in DHS leave it too easily opened.

Both are inherited in an autosomal dominant pattern, which means a single changed copy from one parent is enough. Each child of an affected person has a 1 in 2 chance of inheriting it. Sometimes the change appears for the first time in one individual, with nobody else in the family affected.

Why is it so often misdiagnosed?

This is worth understanding, because it explains a lot of what may have happened to you already.

DHS looks, on ordinary tests, very like hereditary spherocytosis. Both cause a mild to moderate haemolytic anaemia, jaundice, an enlarged spleen and gallstones. Both run in families in the same dominant pattern. The standard screening test for spherocytosis, the EMA binding test, can be abnormal in DHS too. It is entirely understandable that the two are confused, and many people with DHS carry a diagnosis of spherocytosis for years.

The consequence is not academic. The treatment for troublesome spherocytosis is removal of the spleen, and in spherocytosis that works well. In DHS the same operation carries a serious risk of blood clots that can appear decades later.

If you have been told you have hereditary spherocytosis, splenectomy has been suggested, and no genetic test has been done — it is reasonable to ask whether DHS has been excluded first. This is one of the few situations in inherited anaemia where getting the label right changes an irreversible decision.

What are the symptoms?

DHS varies enormously, even between people in the same family carrying exactly the same gene change. Some people are diagnosed only because a blood test done for another reason looked odd. Others have a lifelong anaemia that needs watching.

The anaemia is usually mild to moderate and causes tiredness, breathlessness on exertion, and a lack of energy. Skin may look pale, which for people with darker skin is often seen best inside the mouth, on the lips or the tongue.

Jaundice — a yellow tinge to the whites of the eyes or the skin — comes from the pigment released when red cells break down. It often comes and goes, and is more noticeable during an illness.

The spleen is often enlarged, occasionally enough to be felt as fullness or discomfort under the left ribs.

Gallstones are common and can appear young, sometimes in childhood. They are made of the same pigment, which is why chronic haemolysis produces them.

Iron overload can occur in DHS and it occurs in people who have never had a single transfusion. This surprises almost everyone and it is covered below.

Before birth, a small number of babies with DHS develop fluid around the lungs, heart or abdomen. This can settle by itself or need treatment, and it does not predict how mild or severe the condition will be later.

Why does iron build up, even without transfusions?

Your body senses that red blood cells are being lost and responds sensibly — for the wrong problem. It cannot tell the difference between cells being destroyed early and cells not being built for lack of materials, so it does the one thing it knows how to do: it turns up iron absorption from food.

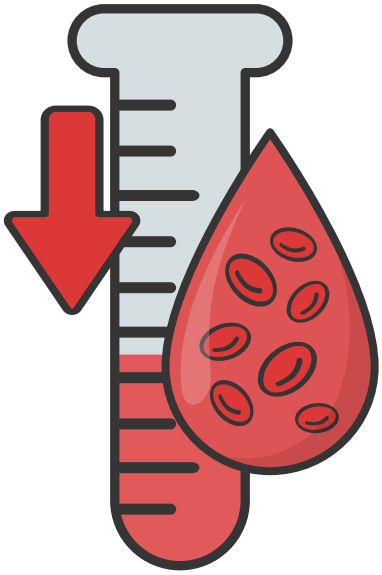
The iron duly arrives. It was never the missing ingredient, so it is not used, and because the body has no way of excreting iron, it accumulates. This continues quietly for years.

You can have a normal or near-normal haemoglobin and still be steadily accumulating iron. The two are not linked in the way people expect, and mild DHS is not protective against it.

Iron overload causes no symptoms until it has damaged something — usually the liver, sometimes the heart or the hormone glands. This is why your team will check it long before you would notice anything, and may recommend treatment while you feel completely well. Our leaflets on iron overload cover this in more detail.

How is DHS diagnosed?

A full blood count often shows a raised MCHC — a measure of how concentrated the haemoglobin is inside the cell. In DHS the cells are dehydrated, so the haemoglobin inside them is packed tighter than normal. It is a small clue on a routine test and it is easily overlooked.



A blood film is examined by a specialist. Stomatocytes may be seen, and so may dense, dry-looking cells with the haemoglobin pushed out to the rim.

The reticulocyte count is usually high, sometimes strikingly so, showing the bone marrow replacing cells quickly. Bilirubin and LDH are raised, reflecting the breakdown.

Ektacytometry, sometimes called LORRCA, measures how well red cells deform under pressure. DHS produces a characteristic curve, and this test is one of the few that reliably separates it from spherocytosis. It is available in specialist centres.

Genetic testing is what confirms the diagnosis. A panel can test PIEZO1, KCNN4 and other red cell genes together. If you have a haemolytic anaemia that has never been fully explained, or a family label that has never been confirmed, this is the test to ask about. This is called the R92 panel and your haematologist should know how to order it.

What is the treatment?

There is no treatment that corrects the underlying gene change, and most people with DHS need no specific treatment at all. Care is mainly about monitoring, managing the complications, and avoiding the things that make it worse.

Folic acid is usually recommended, as the bone marrow is working harder than normal and uses more of it.

Blood transfusions are rarely needed. Some people need them in infancy, or during an illness, around surgery, or through a pregnancy.

Monitoring and treating iron overload is a central part of care. Iron is checked with blood tests, ferritin and transferrin saturation, and with MRI scanning of the liver, which measures it directly and far more accurately. If iron is building up, it can usually be removed by venesection — taking off a unit of blood, exactly like donating. This is simple and effective and is the usual approach in DHS, because most people are not anaemic enough for it to be a problem. If you are too anaemic for venesection, iron chelation medicines are used instead.

Gallstones, if they cause pain or infection, are treated by removing the gallbladder. This operation is safe in DHS. If it is being planned, make sure the surgical team knows the spleen must be left alone — there is a longstanding habit of removing both together, and in DHS that is the wrong thing to do.

Why the spleen must not be removed

In most inherited haemolytic anaemias, taking out the spleen reduces the destruction of red cells and improves the anaemia. It is a reasonable and often successful operation. In DHS it is not.

People with DHS who have had a splenectomy have a markedly increased risk of blood clots — in the deep veins, in the lungs, and in the veins of the liver. The risk does not appear immediately. It can emerge ten, twenty or thirty years afterwards, long after anyone has connected the two, and it can cause pulmonary hypertension, a serious raised pressure in the blood vessels of the lungs.

Removing the spleen does improve the anaemia in DHS. That is precisely the trap: the operation appears to work, and the price is paid decades later.

If splenectomy is ever suggested to you, ask for it to be discussed with a haematologist who knows about DHS before anything is arranged. If you have already had your spleen removed, tell your haematology team — you may need monitoring for pulmonary hypertension and advice about preventing clots, particularly around surgery, pregnancy and long periods of immobility.

What does it mean for my family?

DHS is autosomal dominant, so each child of an affected parent has a 1 in 2 chance of inheriting the gene change. It affects males and females equally.

What is much harder to predict is how it will show itself. Two people with the identical change can have very different degrees of anaemia, and relatives who have always considered themselves well are sometimes found to be affected once anyone looks. It is worth mentioning the diagnosis to your family, particularly to anyone with unexplained anaemia, jaundice or gallstones.

Once the change is identified in one person, testing relatives becomes straightforward. There is a specific reason this matters in DHS: a relative who does not know they have it may be offered a splenectomy for a presumed diagnosis of something else.
A referral to a genetic counsellor is worth asking for. Our leaflet on preimplantation genetic diagnosis (PGD) covers the options for people planning a pregnancy.

What can I do to help myself or my child?

Make sure the diagnosis is genetically confirmed, and make sure it is written down somewhere it will be found. The single most useful thing you can do with this diagnosis is ensure that a surgeon who has never met you before knows not to take out your spleen.

Keep up with iron monitoring, including scans, even when you feel well. Especially when you feel well. This is the part that is easiest to let slide and hardest to undo.

Do not take iron supplements or multivitamins containing iron unless your haematologist has specifically told you to. Anaemia usually does mean iron deficiency, so a doctor who does not know your diagnosis will reasonably reach for iron. Check the labels of over-the-counter supplements, as iron appears in many products that are not obviously iron tablets.

Tell any doctor treating you about the diagnosis, particularly before surgery and in pregnancy. Pregnancy in DHS is usually successful but should be managed with a haematologist involved, as the anaemia can worsen and there is some added risk of clots.

Be careful with alcohol, which adds to the strain on a liver that may already be handling excess iron.

If your child has this condition, tell their school — about the tiredness as much as the appointments.

Most people with DHS live full, normal lives, and many need no treatment at all. The condition is mainly managed by knowing what it is and avoiding the wrong turnings.

When to seek medical advice

Contact your team if you notice:

- Worsening tiredness or breathlessness
- Increasing yellowness of the skin or eyes
- Dark urine
- Pain in the upper right abdomen, which may be gallstones
- That you are pregnant or planning a pregnancy
- That any operation is being planned, particularly one involving the spleen
- That another doctor has prescribed you iron

Seek urgent medical help if you develop swelling or pain in a leg, sudden breathlessness, or chest pain, as these may be signs of a blood clot.

Can we help?

CAN (Congenital Anaemia Network) is a charity specifically for patients with inherited anaemias. It was started by a group of patients and doctors, working together to tackle some of the problems of having an inherited anaemia – the lack of information and the loneliness of not knowing anyone else with your condition. We run events for patients to meet each other, as well as provide some additional information, support and services for patients who need that extra bit of help.

If you want to know more visit www.togetherwecan.uk or email us: info@togetherwecan.uk

Do you know your care should involve a specialist centre for inherited anaemias? These conditions are rare enough that few doctors see many of them and all patients with rare inherited anaemias should be under the care of a haemoglobinopathy specialist. Please read our 'How red cell services are organised in England' information sheet. If you don't know who your specialist service should be, please get in touch with us so we can help you find out.