Gilbert's syndrome

BRITISH LIVER TRUST

Pioneering Liver Health

Gilbert's syndrome

The British Liver Trust works to:

- support people with, and affected by, liver disease
- improve knowledge and understanding of the liver and related health issues
- encourage and fund research into new treatments
- campaign for better services.

All our publications are reviewed by medical specialists and people living with liver disease. Our website provides information on all forms of adult liver disease and our Helpline gives advice and support on enquiries about liver health. Call the Helpline on **0800 652 7330** or visit **britishlivertrust.org.uk**

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The liver

Your liver is your body's 'factory' carrying out hundreds of jobs that are vital to life. It is able to repair itself (even renewing large sections). **However, the liver's ability to repair itself is limited, and continuous injury can lead to permanent scarring.** Your liver is very tough and able to function even when most of it is damaged, which means you may not notice any symptoms for some time.

Your liver has around 500 functions.

Importantly it:

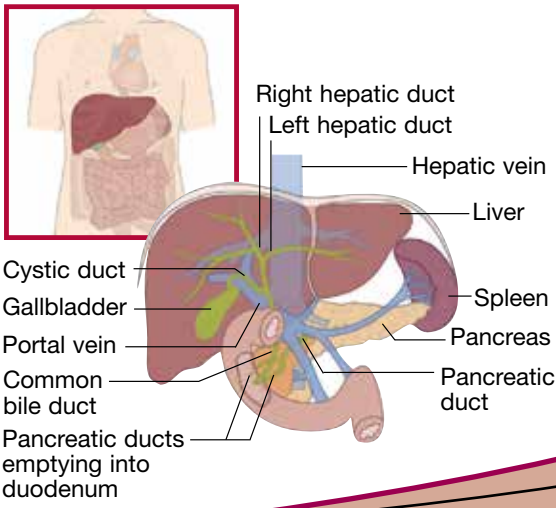
- filters and cleans the blood
- fights infections and disease
- destroys and deals with poisons and drugs
- makes vital proteins which make your blood clot when you cut yourself
- produces bile to help break down food in the gut
- processes food once it has been digested
- stores energy that can be used rapidly when the body needs it most
- regulates fat breakdown and distribution in the bloodstream
- stores sugars, vitamins and minerals, including iron
- gets rid of waste substances from the body
- produces and maintains the balance of hormones
- produces chemicals – enzymes and other proteins – responsible for most of the chemical reactions in the body, for example, repairing tissue
- repairs damage and renews itself (up to a point).

How liver disease develops

Your liver responds to harm by becoming inflamed. Any inflammation of the liver is known as hepatitis, whatever its cause. Sudden inflammation of the liver is known as acute hepatitis. Where inflammation of the liver lasts longer than six months, the condition is known as chronic hepatitis.

Inflammation is part of the process of repairing damaged tissue. In a similar way to a scab forming over a skin wound, a temporary fibrous 'scaffold' forms while liver cells regenerate. If your liver is repeatedly harmed, new liver cells cannot regenerate fast enough and the fibrous tissue remains as a scar. This is called fibrosis and can take a variable amount of time to develop.

When fibrosis is present, the liver may be able to keep functioning quite well. Removing or treating the cause of the inflammation may reverse some, or all, of the fibrosis and prevent further liver damage.

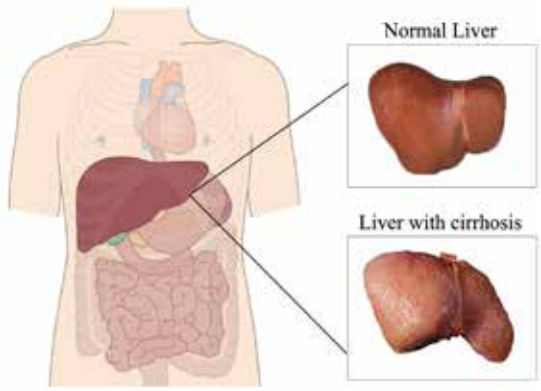


If damage continues, the inflammation and fibrosis can spread throughout your liver, disrupting its shape and affecting the working capacity of liver cells. Even at this stage, people can have no signs or symptoms.

The scar tissue in cirrhosis interrupts the blood flow through the liver. As a result, the blood pressure in the veins around your gut is increased and may result in bleeding. Scar tissue in cirrhosis is difficult to remove and may be permanent. However, further progression can be halted and your cirrhosis stabilised, if the cause of the liver damage is removed.

Cirrhosis increases your risk of liver cancer and can lead to liver failure. If damage to your liver continues, it will become unable to function sufficiently (decompensated) and start to fail; this is sometimes referred to as end stage liver disease. At this stage chemicals and waste products can build up in the body, commonly causing jaundice (yellow colouring of the skin and the whites of the eyes), ascites (a collection of fluid in the abdomen) and hepatic encephalopathy (confusion and altered behaviour), see 'Useful words' section for more information, page 14.

In the final stages of liver disease, the build-up of waste products may lead to multiple organ failure and loss of life.



What is Gilbert's syndrome?

Gilbert's syndrome (GS) is a condition in which you have higher than normal amounts of bilirubin in your blood.

The medical name for this is 'unconjugated hyperbilirubinemia'. It is also sometimes called familial nonhaemolytic bilirubinaemia or constitutional hepatic dysfunction.

These long names may not sound promising but GS is in fact a harmless condition. It is not a disease and it is possible that you may not even know you have it.

GS is usually discovered by chance when a routine or unrelated blood test reveals a rise in the level of bilirubin in your blood. It is likely you will be told that you have high or raised 'serum bilirubin'.

This is not a bad thing in isolation, but until GS is specifically diagnosed you may be left to worry whether having high bilirubin is an indication of a more serious liver illness.

Although a benign condition, people do report some ill-effects from GS. These may or may not be related to other problems. This leaflet describes some of the symptoms most commonly mentioned and provides advice on how you might avoid these symptoms occurring.

What is bilirubin?

Bilirubin is a normal by-product of the breakdown of old red blood cells. These contain haemoglobin, an important protein that helps transport oxygen around

your body. It is also a pigment that gives red blood cells their colour.

Red blood cells last about 120 days. When they expire the haemoglobin is broken down into haem and globin. Globin is a protein that is stored by the body for later use. Haem (or heme) is waste material that needs to be flushed from the body. The 'pathway' or removal process that makes this possible is called glucuronidation.

In this process the heme is broken down into an orangey-yellow pigment known as 'free' bilirubin. This is a fat-soluble form of bilirubin that is transported to your liver. Here, bilirubin is metabolised by a liver enzyme called urodine diphosphate glucuronosyltransferase (more easily called UGT) and modified to a water-soluble form. This is known as 'conjugated' bilirubin.

This watery version is more easily secreted into bile, a fluid produced by your liver to aid digestion. It travels in the bile through your gall bladder and into your small intestine, where it is converted by bacteria into a variety of pigment substances, primarily urobilinogen. It is eventually excreted from the body in your faeces and urine.

This is how the removal of bilirubin is supposed to work. If you have GS, however, you do not have enough of the UGT enzyme to modify the bilirubin at the normal rate.

This is what causes levels of unmetabolised or 'unconjugated' bilirubin to build up in your blood. When testing for bilirubin, a special dye (called a reagent) is added to the blood specimen. Water-soluble conjugated bilirubin will react directly to the addition of

dyes by changing colour. Unconjugated bilirubin, which does not dissolve in water, does not react to the dye until alcohol is added to the solution.

For this reason, unconjugated bilirubin is known as 'indirect' bilirubin and its conjugated form as 'direct' bilirubin. Added together, they are known as your total serum bilirubin.

Who gets Gilbert's syndrome?

GS was first identified by the French doctors Nicolas Augustin Gilbert (after whom it is named) and Pierre Lereboullet in 1900. They described a syndrome of benign, periodic but chronic jaundice occurring without any other symptoms of liver disease.

Today, GS is relatively common. It is thought to affect about one person in 20 or about 4% of the population. Some estimates are higher. It affects both males and females.

GS is thought to be hereditary, meaning that it is caused by a gene that runs in your family.

Genes contain the instructions for making up your body. GS is caused by a variant gene that has a 'mutation'. A mutation is a permanent change in the code of the DNA making up a gene or chromosome. This can alter the way a physical characteristic is expressed or cause some function in the body to occur differently. Sometimes the word 'variant' is used instead of mutation as many changes do not cause any disorder.

In GS the mutation causes 'reduced gene expression', meaning that it limits production of the

specific UGT enzyme (called UGT1A1) responsible for conjugating bilirubin.

This mutation has been pinpointed to occur on a gene called the UDP-glucoronosyltransferase gene. Half the general population may have this gene.

However, GS is a 'recessive' disorder, meaning that you need to have two copies of the abnormal gene (one from each parent) to acquire it. People who inherit the same mutated gene from both their parents are termed 'homozygote'. Even so, having two abnormal genes does not necessarily mean that you will go on to develop GS.

Although it is not understood why, some people with only a single abnormal gene ('heterozygotes') have higher than usual levels of unconjugated bilirubin but do not have GS.

At present there is no established genetic test for GS.

Symptoms

A significant increase in your bilirubin levels may lead to jaundice. This is a yellowing of the skin and the whites of the eyes. In GS this is seen more in the eyes. As bilirubin levels are usually only slightly increased it is likely to take a medically trained person to observe jaundice in your skin appearance.

Jaundice may become more obvious if you become stressed, ill with an infection (particularly a viral illness), starved or dehydrated – conditions not in themselves related to the disorder. Menstruation might also be a factor in sparking off higher bilirubin levels.

While jaundice is the only recognized clinical symptom, many people with GS report a number of common symptoms or effects they attribute to the disorder. This is why they may have a blood test in the first place. Such symptoms include:

- feeling tired all the time (fatigue)
- loss of appetite
- nausea or dizziness
- abdominal pain
- irritable bowel syndrome (IBS)
- difficulty maintaining concentration
- very dark urine.

Such symptoms appear to occur in varying degrees (and some are common to many liver diseases). At least 30% of people with GS do not show any symptoms at all.

Diagnosis

GS is often diagnosed in your late teens and early twenties. In most cases doctors should be able to establish diagnosis on the basis of liver function tests (LFTs) and jaundice, if you have it.

Sometimes – but rarely – a blood test is taken before and after a 48 hour diet in which you are required to reduce your calorie intake. In people with GS a significant increase in their bilirubin levels is usually seen to follow this.

Liver function tests are used to indicate whether your liver is inflamed (hepatitis), damaged or not working properly. They measure levels of certain

enzyme and protein substances in your blood that may alter when liver damage is present.

Liver function tests also measure the amount of bilirubin to gain an indication of your liver's ability to metabolise and secrete it into bile. The 'serum bilirubin test' is considered to provide a very accurate picture of how well the liver is functioning.

Raised and heavily unconjugated bilirubin in your blood is abnormal. When this is the only abnormal result, it is seen as a strong indication that you may have GS. Bilirubin levels can, however, fluctuate in GS and it is possible that they can be within the normal range over a period of time.

Bilirubin is measured in micromoles per litre (umol/L). Total serum bilirubin higher than 17 umol/L is outside the normal range.

Where jaundice is evident, medical staff may seek diagnosis by excluding more serious forms of liver disease. GS is one of the most common causes of unconjugated hyperbilirubinemia, but there are others. These include a rare and dangerous disorder called Crigler-Najjar syndrome which is inherited from the same gene.

If your diagnosis involves further testing or delay of some sort you may experience some anxiety before other possibilities can be ruled out.

For this reason it is important that doctors diagnose GS as soon as possible.

Prevention

Other than inheriting the abnormal gene there are no known risk factors for developing GS. It is not related to any lifestyle habits or caused by any specific environment.

Your doctor should consider the effect of GS when prescribing medicines. Although it is uncommon, there is a possibility that lack of the UGT enzyme can have an effect on the way you respond to certain medications.

Looking after yourself

Having GS should not prevent you leading a normal life in any way.

There are a number of circumstances that are considered likely to cause your bilirubin levels to rise. Some of these cannot be helped but you might manage your situation better if you can avoid the following:

- dieting or fasting
- dehydration
- emotional stress or anxiety
- infectious illnesses
- heavy physical exertion that can leave you feeling drained
- lack of sleep.

It is important that you:

- eat regularly and healthily
- drink plenty of water
- avoid fatty or sugary foods.

Many people find that they cannot tolerate eating carbohydrate foods very well. Typical carbohydrates are bread, pasta, rice and potatoes.

A number of foods, vitamins and supplements are commonly recommended by people with the disorder. You can get more information about diets that have helped others by visiting the websites listed on page 17 ('Useful websites').

Alcohol
There is no clear agreement about the impact of alcohol on people with GS although a number of people report increased sensitivity to its effects.

In general, any person with a liver condition should approach alcohol with caution.

Useful words

Acute – a short sharp illness that may be severe but from which most people will recover in a few weeks without lasting effects.

Benign – a mild condition or disease that is not life-threatening.

Bile – a yellow/green fluid made by the liver containing chemicals to help digest foods containing fat and cholesterol, as well as waste products for removal (excretion) via the bowel.

Carbohydrate – a substance that provides energy or fuel for your body. 'Simple' carbohydrates are sugars, as found in fruit, honey and jam. 'Complex' carbohydrates are

starches, as found in bread, rice and potatoes.

Chromosome – a single, long molecule of DNA that holds our genes, contained within the nucleus of a cell.

Chronic – an illness that lasts a long time (more than six months), possibly for the rest of a person's life.

DNA – deoxyribonucleic acid, the chemical compound of which chromosomes are made and which contains the genetic instructions for the making of proteins in your body.

Enzyme – a substance, usually a protein, produced by the body to help speed up a chemical reaction (which can be measured with liver function tests).

Expression – the process where information encoded in a gene is converted into the structures and functions of a cell.

Haemoglobin – an iron-containing protein (metalloprotein) contained in the red blood cells. Haemoglobin is responsible for transporting oxygen from the lungs to the rest of your body. It is also the pigment that provides the colour of red blood cells.

Hepatic – anything relating to the liver.

Jaundice – a condition in which the whites of the eyes go yellow and in more severe cases the skin also turns yellow. This is caused by a rise of

bilirubin (containing yellow pigment), a waste product which is normally disposed of by the liver.

Metabolism – the physical and chemical processes by which food is transformed into energy. This occurs by absorbing substances and using them in the body or by removing toxins and disposing them from the body as waste product.

Mutation – an occurrence where a gene undergoes a change or variation in the base sequence of its DNA. Some mutations result in the gene no longer coding for the correct protein, or producing a reduced amount of the protein.

Protein – the active molecule in cells that determines the physical structure of the organs and tissue that make up your body. Proteins also control the biological and chemical reactions within your body.

Serum – more than half of your blood is made of plasma which carries the circulating blood cells and platelets. Normally clear or yellowish, serum is the liquid that separates from blood when clotting occurs. Many chemical tests are carried out using serum.

Syndrome – a group of symptoms occurring together to describe a specific disease or condition.

Variant – as in gene variant, a term that may be used in place of 'mutation' (see page 9) as many gene changes do not cause any disorder.

Special thanks

Dr Mark Wright, Consultant Hepatologist, University Hospital Southampton NHS Foundation Trust

Further information

The British Liver Trust publishes a large range of leaflets about the liver and liver problems written for the general public.

Leaflets that you may find particularly helpful include:

- *Diet and liver disease*
- *Liver disease tests explained*

Contact us for more information:
Tel: 01425 481320
Helpline: 0800 652 7330
Email: info@britishlivertrust.org.uk
Web: britishlivertrust.org.uk

We hope you have found this publication helpful.

All our publications are reviewed by medical experts and people living with liver disease. If you have any feedback on this publication please email the Trust at **info@britishlivertrust.org.uk**

The British Liver Trust is proud to be recognised as a provider of expert liver health information, but to do this we must depend on the kind donations of our supporters. The Trust receives no government aid, yet strives to fill the growing need for liver health information in the UK.

We are a small charity, and your donation can make an important difference.
A gift of £5 could help us answer patient calls to our helpline

A gift of £20 could help us to set up a new patient support group

A gift of £50 could support the costs of a new patient guide or leaflet

Gifts can be made:
Online at **www.britishlivertrust.org.uk/donate**
Remember to indicate your Gift Aid preference.

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If you have questions about making a donation, please call **01425 481320** or email **fundraising@britishlivertrust.org.uk**

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Email us: info@britishlivertrust.org.uk
Visit our website: britishlivertrust.org.uk
Write to us: **British Liver Trust**, 6 Dean Park Crescent, Bournemouth BH1 1HL

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