CONDITION

Chronic familial

Learn about inherited causes of long-term or recurring jaundice, including Gilbert syndrome and other familial bilirubin disorders.

WHAT IT IS
Inherited disorder of bilirubin processing

BODY SYSTEM
Digestive

MAIN SYMPTOMS
Yellow eyes, yellow skin, recurring jaundice, dark urine

WHAT CAUSES IT
Inherited gene variants

HOW IT IS DIAGNOSED
Bilirubin blood tests, genetic testing

MAIN TREATMENT
Supportive or specialist bilirubin-lowering treatment

CAN IT BE CURED?
No, no curative treatment is described

IS IT AN EMERGENCY?
Sometimes, confusion or extreme sleepiness with jaundice

LONG-TERM OUTLOOK
Usually favorable, but severe forms can cause brain damage or death

Overview

"Chronic familial" is an incomplete, older medical label. When it appears with the term "icterus," it usually refers to chronic familial jaundice or an inherited condition that affects how the body processes bilirubin. Icterus is another word for jaundice.

Bilirubin is a yellow substance formed when the body breaks down old red blood cells. The liver normally takes bilirubin from the blood, changes it into a form that can leave the body, and sends it into bile. Bile then passes through the intestines and leaves the body in stool.

If one of these steps does not work normally, bilirubin can build up. This may cause yellowing of the whites of the eyes or skin. A blood test may find increased bilirubin even when no yellowing is visible.

Several inherited conditions can cause recurring or persistent bilirubin elevation:

These conditions are different from jaundice caused by hepatitis, gallstones, blocked bile ducts, medication effects, or increased breakdown of red blood cells. For that reason, a new or unexplained bilirubin elevation should not automatically be assumed to be inherited.

- Gilbert syndrome mildly reduces the liver's ability to process unconjugated bilirubin. It is common, usually harmless, and often discovered by chance.
- Crigler-Najjar syndrome causes a more serious reduction in the same processing step. It is rare and usually identified during infancy or childhood.
- Dubin-Johnson syndrome and Rotor syndrome affect the handling of conjugated bilirubin, which is bilirubin that the liver has already processed. They usually cause long-term or recurring jaundice without major liver damage.

Symptoms

Symptoms depend on the specific condition and the bilirubin level. Some people have no symptoms and learn about the condition after routine blood testing.

Possible features include:

Gilbert syndrome often causes only mild, occasional yellowing of the eyes. Episodes may become more noticeable during an illness, dehydration, fasting, strenuous exercise, lack of sleep, or physical stress. These triggers do not usually mean that the liver is being damaged.

Unconjugated bilirubin, the type elevated in Gilbert syndrome, does not pass into urine. Therefore, clearly dark urine is not a typical feature of Gilbert syndrome and may need another explanation. Dark urine can also result from dehydration, blood in the urine, medication, or conjugated bilirubin.

Crigler-Najjar syndrome can produce marked jaundice beginning soon after birth. Very high unconjugated bilirubin can enter the brain and injure nervous tissue, especially in babies. This is known as bilirubin encephalopathy or kernicterus.

Dubin-Johnson and Rotor syndromes usually cause mild, persistent or intermittent jaundice. Urine may become dark because conjugated bilirubin can pass through the kidneys. Itching and pale stools are not typical and may point to a different liver or bile duct problem.

Seek emergency care for jaundice accompanied by confusion, extreme sleepiness, fainting, new difficulty speaking or moving, a high fever with severe upper abdominal pain, or repeated vomiting with an inability to keep fluids down.

A newborn with yellow skin or eyes needs prompt medical assessment. Newborn bilirubin

levels can rise quickly, and appearance alone cannot show whether the level is safe.

- Yellowing of the whites of the eyes
- Yellow or golden skin
- Episodes of jaundice that come and go
- A blood test showing elevated bilirubin
- Dark urine in disorders that raise conjugated bilirubin

Causes and risk factors

Inherited bilirubin disorders are caused by gene variants that change proteins involved in bilirubin processing or transport.

Gilbert syndrome is linked to reduced activity of UGT1A1 , a liver enzyme that changes unconjugated bilirubin into conjugated bilirubin. Because the enzyme still has some activity, the elevation is usually mild. The inheritance pattern and specific UGT1A1 variants can differ among populations.

Crigler-Najjar syndrome also involves UGT1A1, but enzyme activity is severely reduced or absent. Type 1 is the more severe form. Type 2 usually retains some enzyme activity and tends to cause lower bilirubin levels than type 1.

Dubin-Johnson syndrome is associated with changes in ABCC2 , a gene needed to move conjugated bilirubin from liver cells into bile. Rotor syndrome is linked to changes affecting the SLCO1B1 and SLCO1B3 transport proteins, which help the liver take up and store bilirubin-related substances.

A person may be more likely to have an inherited bilirubin disorder if close relatives have unexplained jaundice or a known genetic diagnosis. However, family history may be absent. Mild conditions can go unrecognized, and relatives may carry a gene variant without knowing it.

Having jaundice during illness or fasting does not by itself confirm Gilbert syndrome. Liver disease, blood disorders, infections, and bile duct obstruction can produce similar findings and may require different care.

Diagnosis

Diagnosis begins with a medical history, physical examination, and blood tests. A clinician may ask when jaundice started, whether it comes and goes, what seems to trigger it, and whether

relatives have similar findings. Medication, supplement, alcohol, travel, and infection histories can also be important.

A bilirubin test is usually divided into:

The pattern helps narrow the possible cause. Gilbert and Crigler-Najjar syndromes primarily raise unconjugated bilirubin. Dubin-Johnson and Rotor syndromes primarily raise conjugated bilirubin.

Other tests may include liver enzymes and measures of liver function. A complete blood count, reticulocyte count, lactate dehydrogenase, haptoglobin, or blood smear may be used to check for hemolysis , meaning unusually rapid breakdown of red blood cells.

In a typical case of Gilbert syndrome, the bilirubin elevation is mild and mostly unconjugated, while liver enzymes, blood counts, and other relevant tests are normal. Imaging is not usually needed when the history and laboratory pattern are clear. Deliberate fasting tests are generally unnecessary.

Genetic testing may help when the diagnosis is uncertain, bilirubin is higher than expected, a rare inherited disorder is suspected, or the result could affect treatment decisions. A specialist may order additional blood or urine tests to distinguish Dubin-Johnson syndrome from Rotor syndrome.

Ultrasound or other imaging may be appropriate when there are signs of gallstones, blocked bile ducts, or structural liver disease. A liver biopsy is not routinely needed for Gilbert syndrome and is rarely required for the other inherited bilirubin disorders.

- Unconjugated, or indirect, bilirubin , which has not yet been processed by the liver
- Conjugated, or direct, bilirubin , which has been processed and can pass into bile or urine

Treatment and management

Treatment depends on the specific disorder and its severity.

Gilbert syndrome usually requires no medical treatment. It does not normally cause progressive liver damage or shorten life. Understanding the condition can help avoid repeated testing when a previously evaluated, typical bilirubin pattern returns.

People with Gilbert syndrome may notice fewer episodes when they:

Reduced UGT1A1 activity can affect the handling of certain medicines. This does not mean that all medicines are unsafe. However, a clinician should know about the diagnosis when reviewing treatment, particularly before medicines known to depend on UGT1A1 metabolism or inhibit this enzyme.

Crigler-Najjar syndrome requires specialist care. Management can include phototherapy, which uses specific light wavelengths to help remove bilirubin. Some forms respond to medicines that increase remaining UGT1A1 activity. Severe disease may require liver transplantation. These treatments must be planned and monitored by clinicians experienced in the condition.

Dubin-Johnson and Rotor syndromes usually do not require treatment directed at bilirubin. Management focuses on confirming the diagnosis, avoiding unnecessary procedures, and checking for another cause if symptoms or test results change.

No one should start, stop, or change a prescribed medicine solely because of jaundice without professional advice. When a medicine may be contributing, a clinician can weigh its benefits, risks, and possible alternatives.

- Drink enough fluids, especially during illness or exercise
- Avoid prolonged fasting or crash diets
- Maintain regular sleep and meal patterns
- Discuss new medicines and supplements with a clinician or pharmacist

Complications

Gilbert syndrome is considered benign. The jaundice may cause concern or self-consciousness, but the condition itself does not usually injure the liver. An important practical issue is that bilirubin elevation could be incorrectly blamed on Gilbert syndrome when another illness is present. New symptoms or a change from the usual test pattern should be assessed.

Crigler-Najjar syndrome has more serious risks. Very high unconjugated bilirubin can damage the brain and cause hearing loss, abnormal muscle tone, movement problems, developmental disability, or death. Careful long-term control of bilirubin is essential.

Dubin-Johnson and Rotor syndromes generally have a favorable outlook and do not usually progress to liver failure. Their main complications are repeated jaundice and potentially unnecessary investigations if the diagnosis is not documented.

Regardless of a known inherited condition, jaundice can sometimes have a separate cause. Pale or clay-colored stool, persistent itching, abdominal swelling, unexplained weight loss, fever, worsening pain, easy bleeding, or a major change in urine color should be discussed with a clinician.

Follow up

People with a confirmed, typical case of Gilbert syndrome may only need routine primary care. Repeat bilirubin or liver testing may be done if symptoms change, a new medicine is started, or another illness could be affecting the liver or blood cells.

Follow-up for Crigler-Najjar syndrome is more intensive and usually involves liver, metabolic, or genetic specialists. Monitoring is tailored to bilirubin control, treatment effects, growth and development, and neurological health.

People with Dubin-Johnson or Rotor syndrome may not need frequent condition-specific testing once the diagnosis is secure. Keeping a copy of relevant laboratory or genetic results can help future clinicians recognize the established pattern.

Arrange routine medical review for jaundice that is new, becoming more frequent, or different from prior episodes. Contact a clinician promptly for dark urine, pale stool, persistent vomiting, fever, abdominal pain, itching, unusual fatigue, or possible medication-related symptoms.

Seek urgent or emergency care for confusion, severe drowsiness, fainting, uncontrolled vomiting, severe abdominal pain with fever, or rapidly worsening illness. Any jaundice in a newborn should be evaluated promptly.

Sources

- Strassburg CP. Hyperbilirubinemia syndromes (Gilbert-Meulengracht, Crigler-Najjar, Dubin-Johnson, and Rotor syndrome). Best Practice & Research Clinical Gastroenterology . 2010;24(5):555-571.
- Sticova E, Jirsa M. New insights in bilirubin metabolism and their clinical implications. World Journal of Gastroenterology . 2013;19(38):6398-6407.
- National Library of Medicine. "Gilbert syndrome." MedlinePlus Genetics . U.S. National Institutes of Health. Accessed March 8, 2025.
- National Health Service. "Gilbert's syndrome." NHS health information. Accessed March 8, 2025.
- MSD Manual Professional Edition. "Inborn Metabolic Disorders Causing Hyperbilirubinemia." Merck & Co., Inc. Accessed March 8, 2025.
- Erlinger S, Arias IM, Dhumeaux D. Inherited disorders of bilirubin transport and conjugation: new insights into molecular mechanisms and consequences. Gastroenterology . 2014;146(7):1625-1638.