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Scientific discussion

Gilbert's Syndrome in therapy. Current Perspectives, Outcomes, and Therapy

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GILBERT'S SYNDROME

Gilbert's Syndrome (GS) is an inherent disease that is caused in the liver. It is a harmless genetic condition in which the liver enzyme (the protein molecule) becomes abnormal and cannot properly process bilirubin (waste due to worn out-red blood cells). It is generally due to a reduced number of chemicals in the liver.

People with this disease experience elevated levels of bilirubin pigment, which may lead to yellowing of eyes and skin.

SYNONYMS OF GILBERT SYNDROME

- constitutional liver dysfunction
- familial nonhemolytic jaundice
- Gilbert-Lereboullet syndrome
- Gilbert's disease
- hyperbilirubinemia I
- Meulengracht's disease
- unconjugated benign bilirubinemia

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.

CAUSES OF GILBERT'S SYNDROME

The only cause of Gilbert's Syndrome is an abnormal UGT1A gene from either parent. This condition affects the liver and gives birth to an excessive amount of bilirubin. There is a presence of a gene in the liver that controls enzyme which breaks down the bilirubin. A person who is having an abnormal gene stores a large amount of bilirubin.

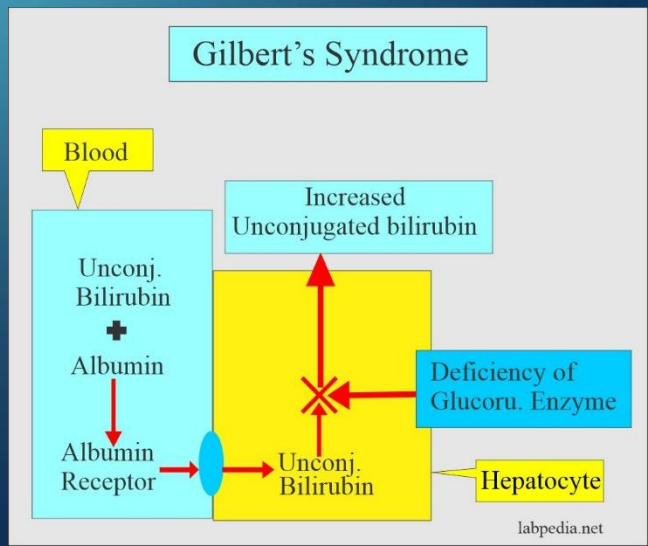
The syndrome is caused by:

- Deficiency of the uridine diphosphate glucuronosyltransferase enzyme or UGT.
- A change of the UDP-glucuronosyltransferase gene – a faulty gene.

PATHOGENESIS OF GS

- During the day, from 200 to 450 mg of bilirubin is formed in the human body. In the blood, bilirubin is present in two fractions - indirect bilirubin (formed during the breakdown of hemoglobin and enzyme systems with the participation of heme, insoluble in water, but well soluble in fats, toxic) and direct (soluble in water, less toxic, excreted from the body with bile). Direct bilirubin is formed in the liver after binding to glucuronic acid, which is why it is also called bound or conjugated.

The key enzyme in this process is uridine diphosphate glucuronyl transferase (UDPGT). Under conditions of UDPGT deficiency, indirect bilirubin cannot be bound in the liver, which leads to its increase in the blood and the development of jaundice



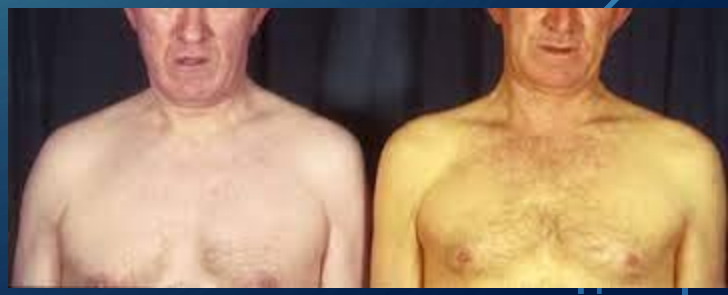
PATHOGENESIS OF GS

- The lack of UDPGT is a hallmark of GS and is associated with mutations of the UGT1A1 gene encoding the enzyme located on the 2nd pair of chromosomes (2q37). In GS patients, the thymidine-adenine (TA) repeat sequence, which serves as the attachment site for DNA-dependent RNA polymerase, contains one extra TA repeat (7 instead of 6). As a result, gene expression is reduced. In the homozygous state, this leads to a decrease in the functional activity of the enzyme by about 30%; in heterozygous carriers, by 14%.
- GS can develop during liver transplantation to a recipient from a donor with a genetic defect. In these patients, after surgery, an isolated increase in bilirubin due to the indirect fraction is detected, which indicates the dominant role of hepatic UDFHT in the metabolism of bilirubin.

SIGNS & SYMPTOMS

- Episodes of mild jaundice may appear in young adults and is more common in males than females.
- Frequently, episodes of jaundice are overlooked.
- Gilbert syndrome is associated with fluctuating levels of bilirubin in the blood (hyperbilirubinemia).
- Bilirubin levels may increase with stress, strain, dehydration, fasting, infection or exposure to cold. In many individuals, jaundice is only evident when one of these triggers raises the bilirubin levels.

Some affected individuals have reported vague, unspecific symptoms including fatigue, weakness and gastrointestinal symptoms such as nausea, abdominal discomfort, and diarrhea.



DIAGNOSIS

- A diagnosis of Gilbert syndrome is often made when blood, drawn for routine health check up or another illness, such as an infection, detects mildly elevated bilirubin levels.
- Because the levels of bilirubin fluctuate, blood tests may not always show elevated bilirubin.

Individuals are determined to have Gilbert syndrome by the presence of hyperbilirubinemia in the absence of hemolysis (premature breakdown of red blood cells) or structural liver damage.

DIAGNOSIS

- General blood and urine tests - the number of immature erythrocytes and slightly reduced hemoglobin are increased in the blood, bilirubin may be present in the urine;
- Biochemical blood test - the sugar level may be slightly reduced, the protein content is within the normal range, ALT and AST are within the normal range, a negative thymol test result;
- Blood test for bilirubin - the total content is increased due to the growth of indirect bilirubin;
- Blood test for coagulability - no deviations;
- Analysis for markers of viral hepatitis - negative.
- Possible tests for serum iron and other tests associated with blood iron.

DIAGNOSIS

- In addition, the patient is required to undergo an ultrasound of the liver in order to exclude the possibility of other hepatic pathologies.
- The size of the liver may increase slightly during periods of exacerbations.
- Molecular genetic analysis of venous blood is rarely performed due to its high cost, but it allows to identify the defective DNA that is the cause of Gilbert's syndrome.

DIAGNOSIS

To confirm the diagnosis, stress tests are performed:

- with starvation - with complete starvation or with caloric restriction, the level of free bilirubin increases by 2-3 times;
- with phenobarbital - after a five-day intake, the level of free bilirubin decreases;
- with nicotinic acid - intravenous injection of the drug increases the level of free bilirubin by 2-3 times;
- with rifampicin - the introduction of the drug leads to an increase in the amount of bilirubin.
- To exclude chronic hepatitis or cirrhosis, a liver puncture may be prescribed

TREATMENT

- Gilbert syndrome is considered harmless, because it does not usually cause any health problems. As a result, no treatment is required.
- Non-drug treatment and prevention of complications of GS include the elimination of risk factors: maintaining a proper lifestyle (giving up bad habits, proper nutrition, etc.), combating stress (autogenic training), and increasing immunity. It is very important for the patient to minimize drug exposure.

TREATMENT

- **Drugs that should be avoided, if possible**, are:
- Atazanavir and indinavir, used to treat HIV infection
- Gemfibrozil, for lowering cholesterol
- Statins, also used for reducing cholesterol, when taken with gemfibrozil
- Irinotecan, used to treat advanced bowel cancer
- Nilotinib, for the treatment of some blood cancers

TREATMENT

- Episodes of jaundice usually resolve on their own without medication. However, if the level of bilirubin exceeds 50 µmol / l and is accompanied by poor health, it is possible to take phenobarbital in a short course (1.5-2.0 mg / kg, or 30-200 mg / day in 2 doses for 2-4 weeks).
- Removal of direct bilirubin is possible with the help of increased diuresis, the use of activated carbon or other sorbents that adsorb bilirubin in the intestine. Through phototherapy, the destruction of indirect bilirubin fixed in tissues is achieved, thereby releasing peripheral receptors that can bind new portions of bilirubin, preventing its penetration through the blood-brain barrier.

DETERRENCE AND PATIENT EDUCATION

- Patients with Gilbert syndrome should be informed about potential triggers such as fasting, intercurrent illness, menstruation, overexertion, hemolytic reactions, and dehydration that may cause a rise in unconjugated bilirubin.
- Avoidance of triggers may be advantageous to reduce anxiety about abnormal bilirubin values. Both patients and their families should be aware of the benign nature of the disorder, its inheritance pattern, and that no treatment is necessary, as outlined above.
- They should also be informed about the excellent prognosis of Gilbert syndrome.

COMPLICATIONS

- Bilirubin is known to exert an antioxidant effect which may be protective.
- Patients with Gilbert syndrome have a lower incidence of ischemic heart disease.
- Studies have also shown a reduction in the incidence of Hodgkin lymphoma, endometrial cancer, and cancer-related mortality when compared to the general population.
- The all-cause mortality rate is lower in individuals with mild hyperbilirubinemia due to Gilbert syndrome compared to the general population.
- Gilbert syndrome patients are at an increased risk of developing gallstones.

Thanks for attention