GILBERT'S SYNDROME: CURRENT INSIGHTS, OUTCOMES AND THERAPIES

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ABSTRACT

Gilbert's syndrome (GS) has been known to clinicians for a long time: more than a hundred years have passed since it was described by Augustine Gilbert in 1901. But in recent years there has been a resurgence of interest in it. This is due to the opened possibility of objective genetic confirmation of the diagnosis and long-term (for several decades) study of its consequences and impact on the health of the population. Clinically manifested usually at the threshold of adulthood, this syndrome is in the field of view of both pediatricians and gastroenterologists-hepatologists working with adult patients, therefore, modern ideas about GS are of interest to a wide range of doctors.

Keywords: *unconjugated hyperbilirubinemia, icterus, uridine diphosphoglucose, liver cirrhosis, aglucones, somatostatin.*

INTRODUCTION

Today, GS is understood as a hereditary disorder of bilirubin metabolism, consisting in the insufficiency of its glucuronidation and the development of unconjugated hyperbilirubinemia.

The characteristic clinical manifestations and data from routine laboratory studies, which served as criteria for diagnosing GS in the pregenetic period, are well known and remain supporting factors for a presumptive diagnosis. For the first time, GS is detected mainly in adolescents of prepubertal and pubertal ages. At the same time,

family history data often indicate a hereditary predisposition. The intensity of jaundice is usually small (subicteric skin, icteric sclera). Hepatomegaly is usually absent. From the laboratory data, an increase in the level of bilirubin (2–5 times) is revealed, mainly due to the free fraction, the activity of ALT/AST is normal, there are no data in favor of hemolytic anemia, markers of viral hepatitis are not detected during repeated studies.

In recent years, it has become possible to objectively confirm the diagnosis using genetic testing. The "genetic face" of SA is currently being studied. It is a mutation in the promoter region of the gene encoding uridine diphosphoglucose (UDP). In this region, responsible for the synthesis of uridine glucuronyltransferase (UGT), the enzyme that “manages” the process of bilirubin glucuronation, an insertion of an additional dinucleotide with a different number of repeats, TA(n), is found. As a result of this mutation, depending on the number of repeats, a large number of alleles arise, of which, along with the classical variant (T1A1), the best known are UGT1A1*28 and UGT1A1*60. The detection of such a mutation makes it possible to unambiguously diagnose GS.

The prevalence of GS in the world is not the same: from 2–5% in the European population to 36% in the African population. However, in recent years there has been an upward trend. Thus, according to our data (children’s hepatitis hospital for 20 years, 1987–2007), the frequency of GS diagnosis as an object of differential diagnosis with viral hepatitis increased by more than 4 times (from 2.8 to 13.6%). And this is in the presence of jaundice, which was the reason for hospitalization, with suspected viral hepatitis. Meanwhile, clinically pronounced jaundice in GS is only the tip of the iceberg. In most people who have a genetic abnormality in the type of GS, jaundice is not pronounced or minimal, and the diagnosis remains unrecognized.

For many years, GS has traditionally been considered benign and does not deserve special attention, since it does not lead to fibrosis and cirrhosis of the liver. However, in recent years, thanks to genetic research, it has become clear that this is not entirely true. It turned out that GS plays a certain role in the formation of cholelithiasis (GSD) in the population. Thus, in a case-control genetic study involving patients with

cholelithiasis (n = 198) and without it (n = 152), it was found that 70% of patients with cholelithiasis are homo- and heterozygotes for GS (p = 0.013), which significantly higher than among individuals without CVD. A particularly serious increase in the incidence of cholelithiasis was noted in men (by 21.2%, p = 0.046) in a larger study (2816 patients with cholelithiasis and 1617 without cholelithiasis).

It is known that cholelithiasis predominantly affects females, but the presence of GS makes men vulnerable as well. Today it can be considered proven that the owners of GS are at risk of developing cholelithiasis.

Another completely new aspect in our ideas about GS was discovered when the study of the characteristics of drug metabolism against the background of GS formed the basis for the emergence of a new direction in pharmacology - pharmacogenetics. This direction is of great importance for the development of drugs and their practical use.

The fact is that the deficiency of glucuronyl transferase (GTP) associated with GS disrupts the metabolism of bilirubin, in particular its glucuronidation, which makes it impossible to excrete bilirubin into the bile ducts and leads to jaundice. There is a whole group of drugs, the so-called aglucones, for the removal of which glucuronidation is also required (for example, salicylates, corticosteroids, sulfonamides, etc.). Competing with bilirubin against the background of GTP deficiency, they cause or increase jaundice. In this regard, the appearance of jaundice during testing of a new drug is a signal for a genetic examination of the patient for GS, since jaundice may be associated not with the hepatotoxicity of the drug, but with the manifestation of GS. So, in the work of J. S. Lee et al. 2 out of 1187 patients treated with tocilizumab had an increase in bilirubin levels. Examination for GS showed that both patients, and only they, had a UGT1A1 mutation. Similar data are given by I. Bernabeu et al. for pegvisomant, used in patients with acromegaly and somatostatin

resistance, the UGT1A1*28 variant prevailed (43%). In such cases, the lack of genetic testing may cause unreasonable doubts about a promising drug. The occurrence of hyperbilirubinemia was also noted against the background of antiviral therapy for chronic hepatitis C with interferon alfa complex with ribavirin, when 2 patients had a 17-fold increase in bilirubin levels and in both of them, a genetic study revealed the classic type of GS (UGT1A1).

The treatment regimen for GS is presented in the work of A.R. Reizis et al. (2011).

1. Liver diet.

2. Mode of sparing: physical and psycho-emotional moderation (no overload); medication regimen - minimization of drugs (glucocorticoids, salicylates, sulfonamides, Diakarb, menthol, etc.).

3. Drug therapy: with a bilirubin level of more than 4-5 norms - phenobarbital in an age dosage; with an increase in the level of bilirubin to 2-3 norms - Valocordin (1 cap / year of life for children and 20-30 caps for adults 3 times a day); UDCA (Ursosan) 10–12 mg/kg/day;

Prophylactic course for 3 months annually (spring-autumn); with an increase in direct bilirubin (up to normalization); in the event of JVP and sludge syndrome (before elimination and 1–2 months after).

Conclusion. Gilbert’s syndrome is a hereditary disorder of bilirubin metabolism, the timely recognition and correction of which is essential both for the patient and for the population as a whole. The current stage in the development of medicine, which made it possible to objectively confirm the diagnosis of Gilbert’s syndrome by genetic methods, puts its diagnosis on a new level. The benign nature of the syndrome, which consists in the absence of fibrosis and outcome in liver cirrhosis, does not exclude such adverse consequences as diseases of the biliary tract up to cholelithiasis. For the prevention and treatment of adverse consequences of Gilbert’s syndrome, it is advisable to use ursodeoxycholic acid (Ursosan).

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