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MINIREVIEWS

Gilbert's syndrome: The good, the bad and the ugly

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Abstract

Gilbert's syndrome (GS) is a common hereditary condition characterized by mild increases in serum bilirubin levels due to inherited defects in bilirubin metabolism. This review, based on peer-reviewed articles spanning from 1977 to January 2024 and sourced through the PubMed platform, provides an overview of current knowledge regarding GS. Early studies primarily focused on defining the clinical and genetic characteristics of the syndrome. More recent research has delved into the genetic mechanisms underlying the reduced expression of bilirubin UDP-glucuronosyltransferase, significantly enhancing our understanding of the pathogenesis of GS. Recent studies have also investigated clinical implications of GS, including its association with metabolic associated steatotic liver disease, cardiovascular disease, mental health and mortality risk, highlighting the complex interplay between genetic factors, bilirubin metabolism, and clinical outcomes.

Key Words: Gilbert's syndrome; Genetic variations; Protective effects; Drug metabolism; Clinical implications

Core Tip: Gilbert's syndrome is a benign hereditary disorder characterized by mild hyperbilirubinemia. This comprehensive review delves into the genetic and environmental determinants of Gilbert's syndrome, elucidating its possible protective role against cardiovascular diseases, metabolic disorders, and certain malignancies, attributed to the antioxidant properties of bilirubin. Additionally, it addresses potential complications during pregnancy and the neonatal period, alongside a possible association with severe schizophrenia. Emphasis is placed on the importance of early diagnosis and patient education to mitigate unnecessary medical interventions and optimize clinical outcomes.

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INTRODUCTION

Hereditary hyperbilirubinemia syndromes encompass a spectrum of conditions characterized by mild increases in serum bilirubin levels due to inherited defects in bilirubin metabolism. Among these syndromes, Gilbert's syndrome (GS) stands out as the most prevalent It was initially described in 1901 by Gilbert and Lareboullet[1,2]. Epidemiological studies indicate that GS affects approximately 2%-13% of the population (Table 1)[3-5], with a higher prevalence observed in individuals without liver disease or hemolysis[6,7]. The hallmark of GS is a notable decrease in hepatic bilirubin UDP-glucuronosyltransferase (UGT) activity, leading to impaired bilirubin conjugation. Despite its prevalence, diagnosing GS remains challenging due to variable diagnostic criteria and the influence of factors such as sex, age, and ethnicity on bilirubin levels. The conventional bilirubin cut-off of 1 mg/dL suggests a 2.5% prevalence, conflicting with the reported 5% prevalence. Inter-laboratory variability further complicates diagnosis. For example, a Czech study found an 8.9% prevalence of GS, higher in men (11.6%) than in women (6.1%)[8]. These findings underscore the necessity for sex-specific and possibly ethnicity-specific diagnostic criteria, considering factors like circadian rhythms, nutrition, and smoking, to accurately understand GS epidemiology.

Clinically, GS typically presents with fluctuating serum bilirubin levels ranging between 1 and 5 mg/dL[6,8], with occasional mild jaundice observed in some patients. However, these elevated bilirubin levels are not associated with clinically significant liver disease[6,9], as evidenced by normal liver enzyme levels and histological findings. Therefore, individuals with GS and isolated unconjugated hyperbilirubinemia typically require no further work-up beyond confirming the absence of liver disease. The prevalence of GS appears to be higher in men compared to women, and fasting has been shown to increase serum bilirubin levels[6,9]. While males are more frequently affected by clinically apparent GS, genetic differences in GS are not considered sex-dependent. The male predominance may be explained by the higher bilirubin load in males and the paradoxical effects of sex hormones on UGT. Furthermore, GS is often diagnosed around puberty, suggesting that hormonal changes significantly influence the syndrome's manifestation and progression[10]. Despite the benign nature of GS, it is crucial to recognize and understand this condition to avoid unnecessary investigations and interventions in patients with isolated unconjugated hyperbilirubinemia.

PATHOPHYSIOLOGY

The pathophysiology of hyperbilirubinemia in GS is multifactorial[11,12], involving disruptions in bilirubin production, hepatic uptake glucuronidation, and transport, all influenced by genetic factors (Figure 1). Individuals with GS exhibit increased bilirubin production from both hepatic and erythroid sources, with evidence of elevated hepatic haem production and occasional haemolysis[13]. Moreover, abnormalities in enzymes involved in haem biosynthesis, such as protoporphyrinogen oxidase, have been reported in peripheral blood cells in GS patients, suggesting a dysregulation in haem metabolism contributing to bilirubin elevation. A key feature of GS is a minimum 50% decrease in hepatic bilirubin UGT activity, leading to impaired bilirubin conjugation[14]. Immunohistochemical studies have demonstrated reduced expression of UGT throughout the hepatic lobule in individuals with GS compared to normal controls. The underlying genetic basis for this reduction involves mutations or polymorphisms in the UGT family 1 member A1 (*UGT1A1*) gene, with homozygosity for the (TA)7TAA variant in the promoter region being particularly prevalent in white populations [15]. Conversely, Asian populations exhibit mutations such as the Gly71Arg mutation (UGT1A1*6) in exon 1 of the *UGT1A1* gene. This highlights ethnic variations in *UGT1A1* gene polymorphisms. Ethnic differences in the prevalence of specific variants, such as varying TA repeat numbers and allele frequencies, are likely to contribute to the heterogeneous presentation of GS across different ethnic groups[14]. Abnormalities in hepatic uptake of bilirubin and potential defects in hepatocellular transport also contribute to the pathogenesis of hyperbilirubinemia in GS[13,16].

Table 1 Prevalence of Gilbert's syndrome by race

Ethnic/Racial group	Prevalence of Gilbert's syndrome
Caucasian (European descent)	2-10%
Africa (Sub-Saharan African)	3-7%
Asian (East Asian: Singapore, Japanese)	2-%
South Asian	Up to 20%
Hispanic/Latino	2.5%
Middle Eastern (Iran)	19%

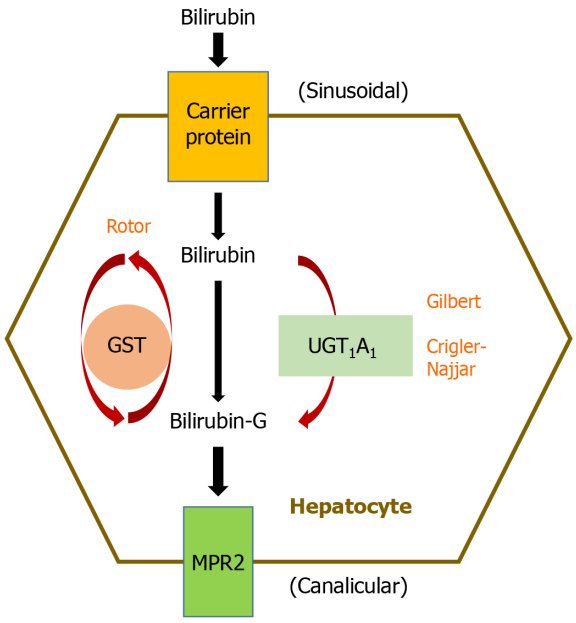

Figure 1 Hepatocyte showing the pathway for bilirubin metabolism. Glutathione-S-transferase is a carrier protein that assists bilirubin uptake into the cytosol of the hepatocyte. GST: Glutathione-S-transferase; Bilirubin-G: Bilirubin glucuronate; UGT1A1: UDP-glucuronosyltransferase family 1 member A1; MPR2: Multidrug resistance -associated protein 2.

CLINICAL PRESENTATION AND DIAGNOSIS

The clinical presentation of GS is variable, characterized by mild unconjugated hyperbilirubinemia without evidence of liver disease or hemolysis. Typically, a patient with GS is asymptomatic, without experiencing abdominal pain, pruritus, pale stools, or dark urine. They may present with intermittent mild icterus which may be precipitated by factors such as periods of fasting, stress, illness, or physical exertion[15,17,18]. Clinical examination is otherwise normal. Diagnosing GS relies primarily on clinical evaluation and laboratory findings. Elevated levels of unconjugated bilirubin on repeated testing are indicative of the condition. Liver function tests are normal, markers of hemolysis are absent, and structural abnormalities are absent, on abdominal ultrasound scanning.

Other tests that are sometimes used to aid the diagnosis of GS are the fasting test, which involves a 24-hour calorie restriction, and administration of rifampicin (rifampicin provocation test) which cause significant increases in serum total and unconjugated bilirubin[7]. Additional diagnostic approaches include measuring bilirubin-UGT activity in the liver, which is typically low in GS patients, but does not always correlate with serum levels. GS can impact neonatal jaundice, particularly in breast-fed neonates. The condition accelerates the onset of jaundice, and interactions with other conditions such as glucose-6-phosphate dehydrogenase deficiency and ABO incompatibility can prolong hyperbilirubinemia in affected infants[15].

MANAGEMENT AND PROGNOSIS OF GS

Management of GS primarily involves reassurance, as no specific treatment or dietary restrictions are necessary due to its benign nature. Once diagnosed, individuals should be informed that GS does not require medical intervention or lifestyle changes. Instead, emphasis should be placed on providing education and addressing any concerns to alleviate

unnecessary patient anxiety[19,20]. The clinical significance of GS lies in the potential for mild hyperbilirubinemia to be mistaken for a sign of liver disease highlighting the importance of accurate diagnosis and patient education[21]. Despite the presence of elevated bilirubin levels, the prognosis for individuals with GS is excellent, with no long-term sequelae reported[22]. In fact, individuals with GS have been reported to have mortality rates that are nearly half those of individuals without the syndrome, suggesting a potential protective effect against all-cause mortality in the general population[20,22,23].

PROTECTIVE EFFECTS OF GS

The antioxidant properties of bilirubin may play a pivotal role in mitigating oxidative stress and inflammation, contributing to its protective effects against various diseases. Research suggests that individuals with GS may have a lower risk of cardiovascular disease compared to the general population, indicating a potential protective role of bilirubin against heart disease[24-27]. Each 1-mmol/L increase in serum bilirubin level has been reported to correlate with a 6.5% decrease in cardiovascular disease risk[28]. Significant reductions in infarct size and lipid and protein oxidation indicate a protective mechanism related oxidative damage[28]. Patients with GS also demonstrate significantly reduced levels of many proatherogenic risk markers in lipid metabolism, including low-density lipoprotein, triacylglycerol, and total cholesterol[27]. Markers of arrhythmia risk, such as P-wave dispersion and QT dispersion, are also reduced in GS compared to healthy subjects, suggesting a potential protective role against cardiac arrhythmias[29]. Elevated serum bilirubin levels, particularly in GS patients, have been associated with a reduced risk of diabetes, metabolic syndrome, and obesity, and some autoimmune and neurodegenerative diseases, which are attributed to its antioxidant and anti-inflammatory properties[30,31]. The relationship between GS and cancer risk is complex. While some studies suggest a reduced risk of colorectal cancer, Hodgkin's lymphoma, and endometrial cancer in GS associations with breast cancer risk are conflicting[32]. Individuals with GS also have higher hemoglobin levels and decreased markers of immune activation, such as white blood cells and platelets, factors that could contribute to better exercise tolerance[33].

EFFECT ON METABOLIC DYSFUNCTION ASSOCIATED STEATOTIC LIVER DISEASE AND OTHER LIVER DISEASES

Recent studies have suggested a potential inverse relationship between unconjugated hyperbilirubinemia and metabolic dysfunction associated steatotic liver disease (MASLD), particularly in the context of GS[34,35]. This phenomenon has sparked interest in understanding the protective effects of unconjugated hyperbilirubinemia against MASLD. Bilirubin, the end product of heme catabolism, is known for its antioxidant, anti-inflammatory, and anti-fibrogenic properties[36], which are believed to play a role in its potential protective effects against MASLD. These properties enable bilirubin to neutralize reactive oxygen species, reduce inflammation, and inhibit the progression of fibrosis, all of which are key factors in the pathogenesis of MASLD[34-36]. This has even led to a concept of inducing an "iatrogenic GS" has been proposed as a potential therapeutic strategy for individuals at high risk for MASLD[37]. This proposes using therapies that decrease hepatic glucuronidation activity, leading to higher levels of unconjugated bilirubin in the bloodstream[37].

The effect of GS on other liver diseases like hepatitis B and C are not well established. However, one study on hepatitis C patients showed that ferritin levels were lower in patients with GS signifying a possible lower level of inflammation in these patients[38]. In another study on patients with hepatitis B infection the presence of GS seemed to improve prognosis [39]. However, conversely in a study on the association of gastro intestinal cancers and the presence of elevated bilirubin showed a positive correlation with incidence of hepatobiliary carcinoma[40]. GS patients do not have an increased risk of cirrhosis overall[41].

DRUG INTERACTIONS IN GS

Clinicians should aware of potential drug-induced liver injury in GS patients. Individuals with GS experience altered hepatic handling of various drugs metabolized by glucuronidation. These include, menthol, estradiol benzoate, lamotrigine, tolbutamide, rifamycin SV, acetaminophen, nonsteroidal anti-inflammatory drugs, statins, gemfibrozil, and human immunodeficiency virus protease inhibitors. While these abnormalities rarely lead to toxicity, individuals with compound *UGT1* genotypes face an increased risk of drug toxicity, for example, with antitubercular drugs and anti-cancer drugs such as irinotecan, and indinavir, an anti-retroviral drug[19,42]. Irinotecan (camptothecin) is an anticancer drug used in metastatic colon cancer and other solid tumors is a good example of this. It is a prodrug and its active metabolite is 7-ethyl-10-hydroxycamptothecin (SN-38). SN-38 is inactivated mainly by UGT, since it has a narrow therapeutic range toxicity can occur in GS patients[43].

GS DURING PREGNANCY AND NEONATAL PERIOD

GS poses various clinical implications, ranging from altered drug metabolism to potential complications during

pregnancy and the neonatal period. Women with GS experience increased frequency and duration of jaundice episodes particularly associated with menstruation abnormalities, oral contraceptive pill use, and cesarean delivery[7]. Exacerbated unconjugated hyperbilirubinemia during pregnancy can sometimes necessitate cesarean section and result in neonatal hyperbilirubinemia, therefore, requiring close monitoring during pregnancy, childbirth and the neonatal period. In neonates, GS, in combination with other factors may cause severe hyperbilirubinemia, potentially leading to complications such as bilirubin encephalopathy[12,44].

IMPACT OF GS ON LIVER TRANSPLANTATION

In liver transplantation, the presence of GS in the donor liver can have implications for post-transplant outcomes[15]. While GS livers can be used for transplantation, there is a risk of post-transplant hyperbilirubinemia when the donor liver carries the GS genotype[45]. This underscores the importance of considering GS as a potential factor for raised serum bilirubin in post-transplant monitoring.

MENTAL HEALTH AND GS

Schizophrenic patients with GS exhibit significant decreases in N-acetyl aspartate/creatine-phosphocreatinine and myoinositol/creatine-phosphocreatinine ratios in the hippocampus, basal ganglia, and vermis of the cerebellum compared to both healthy subjects and schizophrenic patients without GS, indicating potential differences in brain metabolism associated with schizophrenia and GS co-occurrence. The findings suggest that schizophrenia in GS represents a more severe subtype of the mental illness[46]. Patients with GS also exhibit specific changes in signal intensity on magnetic resonance imaging (MRI), showing decreased signal intensity on T1-weighted MRI and increased signal intensity on T2-weighted MRI in various brain regions, such as, the frontotemporal cortex, limbic system, and basal ganglia[47].

CONCLUSION

GS is considered a benign genetic disorder characterized by mildly elevated levels of unconjugated bilirubin. The pathophysiology of hyperbilirubinemia in GS involves disruptions in bilirubin production, hepatic uptake, and glucuronidation, and transport, all of which are influenced by genetic factors. The diagnosis is essentially clinical and patients should be re-assured as to the generally benign nature of the condition. Although typically asymptomatic, there is emerging evidence that GS as clinical implications. These include reduction in all-cause mortality, and protective effects against cardiovascular disorders, metabolic conditions, including type 2 diabetes and metabolic associated steatotic liver disease, and some malignancies. However, the presence of GS may sometimes impact negatively on pregnancy and the neonate, especially in relation to neonatal hyperbilirubinemia. The condition may also be associated with more severe forms of schizophrenia. The underlying mechanisms for these effects are still far from clear but may include genetic factors and the anti-oxidant and anti-inflammatory properties of bilirubin.

FOOTNOTES

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