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Gilbert's Syndrome
Gilbert's Sendromu

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ABSTRACT

Gilbert's syndrome is a benign condition that does not progress to chronic liver disease or fibrosis. Gilbert's syndrome diagnosis should be considered in patients with chronic elevation of unconjugated bilirubin. In these patients the presence of hemolysis and other diseases of the liver should be excluded. Gilbert's syndrome is an autosomal recessive disease. The mutation of uridine diphosphate glucuronyl transferase is seen in 10-16% of the population. There is a 70-80% decrease in bilirubin glucuronidation. In cases of unexplained indirect hyperbilirubinemia with no history of drugs, smoking or alcohol use, Gilbert's syndrome should be considered. Firstly, hemolysis should be excluded. It has been reported that having increased levels of indirect bilirubin lowers the incidence of carotid plaque and coronary artery disease in patients with Gilbert's syndrome. The antioxidation and resistance to oxidative stress status of patients with Gilbert's syndrome is known to be high. However, Gilbert's syndrome is associated with breast and colon cancer. Several studies have reported that liver transplantation from a patient with Gilbert's syndrome had no harm to himself or to the recipient. An exact relationship between schizophrenia and Gilbert's syndrome has not been demonstrated. Gilbert's syndrome patients have a risk of breast and colon cancer so frequent follow up is recommended.

Key words: Gilbert's syndrome, bilirubin, uridine diphosphate glucuronyl transferase, cancer.

ÖZET

Gilbert's sendromu benign seyir göstermekte olup kronik karaciğer hastalığı ve fibrozis görülmemektedir. Gilbert's sendromu tanısı kronik indirekt bilirubin yüksekliği olan hastalar da düşünülmelidir. Bu hastalarda hemoliz varlığı ve karaciğerin diğer hastalıkları ekarte edilmelidir. Gilbert's sendromu otozomal resesif geçiş gösterir. Üridin difosfat glukuronil transferaz enzim mutasyonu toplumda %10-16 görülmektedir. Bilirubin glukuronidazyonunda %70-80 azalma görülür.

İlaç, sigara, alkol kullanımı yokken açıklanamayan hiperbilirubinemi durumlarında Gilbert's sendromu akla gelmedidir. Öncelikle hemoliz dışlanmalıdır. Gilbert's sendromu hastalarında normalin üstündeki indirekt bilirubin artışının karotid plak ve koroner arter hastalığının insidansını düşürdüğü bildirilmiştir. Gilbert's sendromu hastalarında antioksidan durumun yüksek olduğu ve oksidatif strese direnç olduğu düşünülmektedir ama kolon kanseri ve meme kanseri ile ilişkilidir. Birkaç çalışmada canlı Gilbert's sendromu hastasının karaciğer dokusunun naklinin Gilbert's sendromu hastasının kendisine veya alıcıya zarar vermediği bildirilmiştir. Şizofreni ile belirgin ilişkisi gösterilememiştir. Gilbert's sendromu hastasında kolon ve meme kanseri riski arttığından sık takibi tavsiye edilebilir.
Anahtar kelimeler: Gilbert's sendromu, bilirubin, üridin difosfat glukuronil transferaz, kanser.

Introduction

Gilbert's syndrome (GS) is a benign condition that does not progress to chronic liver disease or fibrosis. GS diagnosis should be considered in patients with chronic elevation of unconjugated bilirubin. In these patients the presence of hemolysis and other diseases of the liver should be excluded. GS was first described in 1901[1]. In 1991 (UGT1A) a subunit of uridine diphosphate-glucuronyl transferase (UGT) and in 1995 a polymorphism of UGT1A1*28 were shown[2]. GS is an autosomal recessive disease[3]. It is an inherited disease as a result of a congenital mutation in the UGT enzyme gene region on chromosome 2q37[4,5]. It is found at rates of 3-17% in the community. It is found at rates of 12.4% in males and 4.8% in females[6]. The prevalence is found to be 5% in people of Asian origin, 10% in people of Caucasian origin and 25% in African-Americans[7]. UGT1A1*28 (+/+) is found in 12% of Scottish people[8], 16% of Europeans[2], 12% of Indians[9], 8% of Egyptians[10], and 23% of African-American subjects[11]. In China and Japan, the frequencies are lower[9].

Usually it does not occur until the adolescence period. It is seen mostly in the 2nd -3rd decade. It mostly gives symptoms after vigorous exercise, stress or when intervening in other disease[12]. Total serum bilirubin levels are usually elevated and range between 1.0-3.0 mg/dL and rarely exceed 5 mg/dL[13]. A complete loss of the enzyme function UGT1 is seen in Crigler-Najjar syndrome in which bilirubin levels exceed 19.5 mg/dL and may cause neurological disorders[14]. The objective of this article is to review GS in the global context especially its cardioprotective effect and increased risk of cancer.

Function of UGT

Normally 90% of bilirubin is unconjugated nonpolar which is found to be bound to albumin[15]. Bilirubin, which is an end product of heme degradation and water insoluble, is a toxic substance. Hepatic glucuronidation of bilirubin which is water insoluble is catalyzed by the hepatic UGT1 enzyme[16]. The enzyme functioning via an ATP-related transporter called MRP2 which is found in bile canaliculi catalyzes glucuronidation[17].

Subgroups of UGT Enzyme

This enzyme related to the membrane-bound superfamily is localized in the endoplasmic reticulum[18,19]. There are 117 members of this family. This family has four subgroups UGT1, UGT2, UGT3 and UGT8[20]. UGT1 is divided into subgroups UGT1A and UGT1B, the UGT1B form primarily metabolizes xeno antibiotics. The distance between the UGT1 enzyme gene complexes exon 1 and exon 2 is about 13 kb and this region is known as the UGT1A1 promoter[21,22]. In this region the 5′ end of a 500 bp area is a transcription starting region which has a few regulatory elements. These are the 'Barbie box', 'activator protein 1' and C-E binding protein[22].

UGT1A is divided into eight isoforms UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A7, UGT1A8, UGT1A9 and UGT1A10. In humans UGT1A1, UGT1A3, UGT1A4, UGT1A6 and UGT1A9 are predominantly expressed in the liver, UGT1A7 in the esophagus and stomach, UGT1A8 in the esophagus and colon and UGT1A10 in the esophagus, stomach, gallbladder, and colon[23].

Polymorphism of UGT enzyme

In Caucasian individuals the homozygous insertion of TA in the TATA-box promoter region of gene UDP1 is responsible for GS[2]. This genotype is known as UGT1A1*28 and occurs as a result of 7 repeats of TA instead of 6 repeats. This mutation is seen in 10-16% of the population[24]. There is a 70-80% decrease in bilirubin glucuronidation[2]. In the African population the repeat of 8 TA is seen as 0.07% and known as UGT1A1*37, in the same population UGT1A1*36 mutation as a repeat of 5 TA is seen as 0.08%[16].

The difference between races is seen in types of polymorphism[11]. It has been shown that the polymorphism of UGT1A6*2 may decrease the glucuronidation and affect the metabolism of

some drugs but because of not functioning in conjugation, the bilirubin conjugation is not affected[25]. The polymorphism of UGT1A1*1-113 enzyme was determined[26].

Diagnosis

There is no indication for liver biopsy in patients with GS. If a biopsy is performed, it will show normal liver tissues[26]. If the patient who presented with hyperbilirubinemia (HB) had a history of the same situation and fluctuation of bilirubin levels would be important. Other causes of indirect HB should be excluded. In cases of unexplained indirect HB with no history of drugs, smoking or alcohol use, GS should be considered[27]. Firstly, hemolysis should be excluded. Serum levels of lactate dehydrogenase should be measured and reticulocyte counts should be performed. After 24 hours of 1680 kJ diet serum the total bilirubin level elevates from 1 mg/dL to 1.5-3 mg/dL[28]. After 24 hours or prolonged fasting bilirubin levels increase[2]. After giving intravenous nicotinic acid the indirect bilirubin level increases but this situation is not specific. This is seen also in chronic liver disease[29]. Mutations in the gene can be detected by polymerase chain reaction (PCR). Routine genetic testing is not recommended[30].

In patients suspected of GS a rifampin test may be performed; this test is highly sensitive and specific[31]. After 4 hours of giving 600 mg of rifampin the serum level of indirect bilirubin was more than 1.3 mg/dl[32]. After 24 hours of orally given rifampin indirect bilirubin was nearly 1.8 mg/dl and after 32 hours it came back normal[12]. Rifampin induces the cytochrome P450 enzyme system so the lack of UGT1 in GS patients increases the serum level of bilirubin.

Differential Diagnosis

GS has a broad differential diagnosis because numerous causes of unconjugated HB must be considered. Hemolysis, breakdown of red blood cells (RBC) leads to increase production of bilirubin .Glucose-6-phosphate dehydrogenase (G6PD) deficiency, a recessive X-linked trait, is the most common enzyme deficiency in the world. The most devastating clinical consequence of this deficit is severe neonatal jaundice, which results in sensorineural deficit, and severe hemolytic anemia[33]. The diagnosis of G6PD deficiency is made by a quantitative spectrophotometric analysis or, more commonly, by a rapid fluorescent spot test detecting the generation of NADPH from NADP[34]. Crigler-Najjar type 1 is characterized by striking unconjugated HB that appears in the neonatal period, persists for life, and is unresponsive to phenobarbital. Bilirubin concentrations are typically lower in Crigler-Najjar type 2, and can be

reduced to 3 to 5 mg/dL by Phenobarbital while plasma bilirubin levels of GS can be normalized by phenobarbital[35]. Also, unconjugated HB of Crigler-Najjar type 1 usually elevated >20 mg/dL and its generally between 6 and 25 mg/dL, but its lower GS than these diseases[36]. Hepatic jaundice can be caused by acute and chronic liver diseases in which liver's ability to metabolize and excrete bilirubin is reduced leading to unconjugated hyperbilirubinemia[37]. These liver diseases show elevation of the laboratory parameters such as liver aminotransferases, alkaline phosphatase, gamma-glutamyl transferase in the contrary they are normal in GS.

Ineffective erythropoiesis leads to rapid lysis of RBC and HB. It can be seen in megaloblastic anemia as in folate or vitamin B_{12} deficiency, iron deficiency anemia, sideroblastic anemia, and polycythemia vera[38]. Infections can cause HB by infecting RBC leading to their destruction or infecting liver and impairing its detoxification function such as malaria, hepatitis viruses, enteric fever, leptospirosis, brucellosis and rickettsial infection[39]. All of the diseases elevate lactate dehydrogenase and reticulocyte count by hemolysis. Increased levels of unconjugated HB with elevated levels of lactate dehydrogenase are considered hemolysis and differentiated form of GS[40]. Corrected reticulocyte counts were performed via reticulocyte smear and its levels of more than 2% were accepted hemolysis[41], therefore, these patients are differentiated form GS.

Congestive heart failure leads to passive liver congestion and acute ischemic hepatitis that impair liver function leading to hyperbilirubinemia[42]. Prosthetic heart valves also can lead to HB by mechanical destruction of RBC. Cardiac diseases may be diagnosed by echocardiogram. Hypermetabolic state of thyrotoxicosis increases hepatic oxygen consumption without an appropriate increase in hepatic blood flow leading to cholestasis and liver dysfunction thus increase bilirubin level[43]. Rhabdomyolysis increase myoglobin level that is metabolized to bilirubin[44]. Serum levels of creatine phosphokinase and lactate dehydrogenase were elevated by rhabdomyolysis. Medications such as probenecid, rifamycin and other antibiotics interfere with the uptake of bilirubin into the liver cells and may cause unconjugated hyperbilirubinemia[45]. Unconjugated HB should improve after withdrawal of offending agent.

GS Reduces the Risk of Heart Disease

It has been reported that having increased levels of indirect bilirubin lowers the incidence of carotid plaque and coronary artery disease in patients of GS. Its preventive effect of

atherosclerotic disease has not been fully understood yet and is thought to be multifactorial[46-48]. Bilirubin circulating in serum is known to be a potent physiologic antioxidant[49]. The antioxidation and resistance to oxidative stress status of patients with GS is known to be high[50].

The role of oxidative stress and inflammatory processes in the etiology of atherosclerotic heart disease is well known. C-reactive protein (CRP) and low density lipoprotein (LDL) levels in patients with GS are lower than in healthy individuals[51]. LDL is known to have a role in the oxidative process. Lipid peroxidation and its end products play a role in the pathogenesis of atherosclerosis[50]. In patients with GS the low levels of LDL and CRP indicate low oxidative stress, strong capacity of antioxidation and low inflammation process. Indeed, previous studies have shown indirect bilirubin to be protective against lipid peroxidation and as a remover of peroxide radicals[52,53].

It has been shown that people with the homozygous mutation of UGT1A1*28 have a low risk of cardiovascular disease[24]. It has been shown that patients with GS related to the *UGT1A1* mutation have a 13% lower risk of myocardial infarction[54]. In the same allele it has been reported the mortality risk to be low after coronary bypass and percutaneous transluminal coronary angioplasty[55].

Low serum bilirubin levels increase aortic stiffness and urinary biopyrrins excretion which have been reported as a risk factor for *cardiovascular* disease[56]. Low bilirubin levels have been found to increase the advanced glycosylation end products[57]. It has been stated that bilirubin is a more potent antioxidant than alpha-tocopherol[58]. Biopyrrins, an oxidative metabolite of bilirubin, shows a feature of a general marker of oxidative stress[59,60]. There are correlations among biopyrrins, 8-hydroxydeoxyguanosine which show oxidative DNA damage and acrolein-lysine as a marker of lipid peroxidation[61,62]. An inverse relationship has been found between serum bilirubin levels and biopyrrins urinary excretion[56]. Interestingly, patients with GS who have plenty of bilirubin as a substrate for biopyrrins have a low urinary excretion. The authors attributed this situation to a cytoprotective effect of bilirubin[63].

Previous study reported that mean platelet volume (MPV) levels of GS patients were found to be significantly lower than control group[64]. High level of MPV is an increase in the incidences of cardiovascular events such as myocardial infarction and acute coronary syndrome. Interleukin-6 cytokine may be suppressed in GS patients due to the antioxidant effect of

bilirubin so decreasing megakaryopoiesis in bone marrow so lowering the release of large-sized thrombocyes to blood as a result decreasing the MPV[64]. Authors reported that the elevated levels of bilirubin and decreasing levels of MPV in GS patients may have an effect on the slowing down of the cardiovascular disease.

Another study reported that the measurements of P wave and QT interval were found to be lower in GS patients compared to the control group[65]. Both P-wave and QT dispersion are known as the difference between maximum interval and minimum interval by electrocardiography. P-wave dispersion can be used to determine the risk of atrial fibrillation. Increased QT dispersion can be seen in many patients suffering from cardiac diseases such as patients with left ventricular hypertrophy, patients with heart failure, including idiopathic dilated cardiomyopathy, patients with acute myocardial infarction, hypertensive patients and patients with aortic stenosis[65]. The decreased MPV, P-wave and QT dispersion in GS patients may be related of diminished cardiovascular events.

Previous study showed that epicardial adipose tissue (EAT) thickness in GS patients was strongly lower than that of the control group. This tissue releases inflammatory cytokines hormones and chemokines. In this study the low EAT thickness in GS group and its relation with bilirubin may demonstrate the cardioprotective effect of bilirubin. Because of low EAT thickness, the released pro-inflammatory cytokines may be low and, as a result, cardioprotective effects may occur[66].

Is There an Increased Risk of Cancer in GS?

In a study of premenopausal African Americans it has been found that occurrence of UGT1A1 promoter polymorphism is associated with breast cancer. Polymorphism of the UDP1 enzyme which catalyzes glucuronidation of 17β-estradiol may alter the activity of steroid hormones as estradiol[67-69]. Polymorphism of UGT1A1*28 in post-menopausal women has been found to increase the risk of invasive breast cancer 1.8 fold[68,70]. The same study has shown that polymorphism of the UGT1A6 promoter may increase the risk of cancer by decreasing the protective effect of aspirin against colon cancer[71]. It has been reported that regarding the elevation of serum bilirubin level, for every 1 mg/dl the risk of non-dermatologic and colon cancer is increasing. The authors defend the view that during the enterohepatic cycle high levels of bilirubin exposure may increase the risk of colon cancer[72]. However, the risk of endometrial cancer does not increase[73].

GS and Drug Metabolism

In 1970 the effect of GS on drug metabolism was described[74]. The UGT1A1 enzyme catalyzes 2-hydroxy-estrone and estradiol glucuronidation. It is also a catalyst for the glucuronidation of ethinyl estradiol, gemfibrozil, irinotecan, simvastatin and buprenorphine[75]. The elimination of SN-48, an active metabolite of irinotecan, is decreased and its toxic effect increases. Neutropenia, thrombocytopenia and diarrhea may be seen[75,76]. Decreasing glucuronidation of acetaminophen, aspirin, coumarin, nonsteroidal anti-inflammatory drugs and dopamine derivatives may cause some disturbances[25,77]. As protease inhibitors indinavir and atazanavir are potent inhibitors of the UDP1 enzyme[78,79]. Other inhibitor drugs of this enzyme are amitriptyline, canrenoic acid, sulfinpirazon and ketoconazole[79,80]. Hyperbilirubinemia may occur while using the drugs simvastatin, atorvastatin, cerivastatin[81], and ezetimibe[82].

GS and Other Metabolic Conditions

It has been found that serum bilirubin level is inversely related to insulin resistance, serum insulin, triglyceride, systolic blood pressure, apolipoprotein B and obesity[53,83,84]. Even though the incidence of cholelithiasis in GS patients has been reported to be high, this increase is more prominent in concomitant conditions like cystic fibrosis, hereditary spherocytosis and sickle cell anemia[85-87].

GS in Newborns

A self-limited indirect HB seen in newborns within the first 5 days is called neonatal jaundice[88]. In newborns UDP1 enzyme maturation may be delayed up to 3 months[89]. Normally in full term infants serum total bilirubin levels may reach a level of 14 mg/dL in the first 72 hours then come down to normal within 7-10 days[90]. In full term infants with breast milk jaundice bilirubin levels may reach up to 36-57.7 mg/dL within the first 10-19 days[91]. In full term infants if the serum bilirubin level is more than 28 mg/dL, a pathological condition should be investigated[92]. GS accelerates development of neonatal jaundice and the emergence of jaundice due to GS 96 hours after birth has been reported[93]. In addition, severe increase in bilirubin levels are not due to GS alone but is reported to be related to concomitant conditions such as G6PD enzyme deficiency, AB0 incompatibility, breastfeeding and pyloric stenosis[94-96].

Can a GS Patient Be a Donor?

Studies have shown that recipients of liver transplants from GS patients showed unexplained HB. Genetic studies have shown that GS can be transferred by liver transplantation and has been reported to be seen in recipients. A limited number of studies have reported that liver transplantation from a patient with GS had no harm to himself or to the recipient[97-99]. Some recipients of liver transplantation from a GS cadaver have been reported to have acute hepatitis due to rejection[97].

Relationship between GS and Schizophrenia

HB is a risk factor for brain damage. Neonatal HB can lead to mental disorders. However, an exact relationship between schizophrenia and GS has not been demonstrated. In this matter magnetic resonance and computer tomography findings in schizophrenia patients with or without GS were compared. GS patient findings were reported to be significant but in the literature only 1-2 studies are available on this subject so new studies are needed on this issue[100-102].

Conclusion

GS does not require treatment. It does not cause hepatic damage. There is no follow-up duration proposed in the literature. It may be appropriate to call a patient suffering from weakness and tiredness back for re-examination. During drug use the frequency of follow ups should be increased. Because of the increased incidence of cholelithiasis, periodic ultrasonography follow up may be recommended.

Caution should be taken in these patients because an increased risk of breast cancer has been reported. Mammography may be recommended before the age of screening of healthy individuals but there is no information in the literature on this issue. GS patients have a risk of colon cancer so frequent follow up may be recommended. There is a need for prospective studies to recommend the frequency of follow up for patients with increased risk of breast and colon cancer.

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