

Familial Association of Gilberts and Beta Thalassemia Trait

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Abstract

A 21 yrs old male from Jatrabari, Dhaka became unfit to travel to Gulf, as his serum bilirubin was found 5.7 mg/dl. He was diagnosed to have Thalassemia trait along with Gilbert's syndrome. His elder brother has also got similar diseases from age 14. Here both associations of these diseases with positive family history are highlighted.

Key words: Gilbert syndrome; thalassemia trait; hyperbilirubinemia; rifampicin test; autosomal recessive disorder; uridine diphosphate glucuronyltransferase.

INTRODUCTION

Gilbert syndrome is the most common inherited disorder of bilirubin metabolism. This disease may be precipitated by dehydration, fasting, or stress, an intercurrent febrile disease or vigorous exercise. Rarely, the disorder occurs with some primary haematological disorder such as α -thalassemia minor (thalassemia trait), glucose-6-phosphate dehydrogenase (G-6 PD) deficiency and hereditary spherocytosis¹. Here, we describe one such patient having GS and thalassemia trait with familial association.

CASE REPORT

A 21 yrs old student was willing to migrate to Gulf countries, but his medical report became unfit as his serum bilirubin was found 5.7 mg/dl. Apart from few days of nausea, patient had no symptoms suggestive of liver diseases. He reported taking no over-the-counter medications. His review of systems was unremarkable. Specifically, he reported no abdominal discomfort; nausea; vomiting; or changes in bowel habits or skin, urine, or stool color.

He reported no known drug allergies. He was a lifetime nonsmoker, had no significant travel and exposure history. But his elder brother, 25 yrs was diagnosed as thalassemia minor and history of fluctuating jaundice since age 14. His Physical examination showed a well-nourished body with normal growth and development. Liver span was normal, but spleen was just palpable. There were no signs of ecchymosis or bruising any where in the whole body.

Laboratory testing showed normal serum chemistry values, renal function, and glucose levels. On examination of peripheral blood smear red blood cells (RBC's) were markedly microcytic and hypochromic. Few target cells were also seen. Mean corpuscular volume (MCV) was 68 fl. On Hb electrophoresis HbA₂ was 4.7%. HbF was normal. Although his aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels had been mildly elevated. His total bilirubin and direct bilirubin values were elevated at 3.8 mg/dL and 0.8 mg/dL, respectively. Gilbert syndrome was suggested, and after 2 day, rifampin test was performed. Total serum unconjugated bilirubin concentrations were measured at baseline and 6 and 24 hours after the administration of oral 600 mg rifampin, showing values of 1.9, 2.9 and 4.4 mg/dl, respectively. Direct and indirect Coombs tests were negative. Abdominal sonogram disclosed splenomegaly (13.3 cm).

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DISCUSSION

This disorder, the most common inherited cause of unconjugated hyperbilirubinemia, was first described by Augustine Gilbert and Pierre Lereboullet in 1901². Later, Arias³ described a disorder in which eight patients with chronic nonhemolytic jaundice had glucuronyltransferase deficiency.

The patient was diagnosed to have thalassemia trait based on profound microcytosis, hypochromia with target cells, mild anemia, raised HbA2 and unconjugated hyperbilirubinemia. GS was diagnosed on basis of unconjugated hyperbilirubinemia, normal values of liver function tests and normal hepatic histology. Diagnosis of GS was further confirmed on subjecting the patient to rifampicin test⁴.

Gilbert syndrome is inherited as an autosomal dominant trait and that patients are heterozygous for a single abnormal gene⁵. Plasma bilirubin level in normal subjects varies with gender; the postpubertal males have higher levels than females⁶ and this may be due to the effect of female hormones on UDP-glucuronosyltransferase^{7,8}. However, the condition is more frequent in males, even allowing for this natural difference, as the reported male to female ratio is 2.7:1.9. The reported prevalence of Gilbert syndrome varies from 3% to 12% in various ethnic groups^{5,8-10}. Because positive family history was reported in less than 4% of patients, 27% to 55% of siblings and 16% to 26% of parents,^{9,10} the familial history cannot be considered an essential part of the diagnostic workup of Gilbert disease.

The genetic basis of the disease was elucidated in 1995¹¹. Decreased hepatic bilirubin uridine diphosphate glucuronosyltransferase factor, though transport abnormality in hepatocytes and occult hemolysis may also contribute.

Recent advances in genetics research have demonstrated that GS is associated with a homozygous polymorphism—A(TA)7 TAA instead of A(TA)6 TAA in the TATA box of the promoter region of the UGT1A1 gene¹², the gene that encodes bilirubin-UGT). The presence of the longer TATAA element in patients with GS results in the reduced expression of a reporter gene. There are two genetic mutations possible in GS¹³. The first clinical phenotype can be described as the polymorphism present in the TATA box promoter region of the UGT1A1 gene, as was the case with our patient. The other variant is caused by missense mutations in the coding region of the UGT1A1.

It is highlighted that the patients with both GS and thalassemia trait have higher bilirubin concentrations because the (TA)7/(TA)7 GS genotype is one of the factors accounting for the hyperbilirubinemia observed in thalassemia major, intermedia, and heterozygous individuals¹⁴.

In conclusion, Gilbert's syndrome should be suspected if the patient has a mild hyperbilirubinemia with a high fraction of unconjugated bilirubin, normal liver function, and no overt signs of hemolysis. But in presence of hemolysis, alternative diagnosis or another association should be sought.

DISCLOSURE

The author declared no competing interest.

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