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Case Report

Gilbert syndrome in a young boy with thalassemia trait: a rare association

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ABSTRACT

Gilbert syndrome (GS) is a mild benign disease characterized by asymptomatic unconjugated hyperbilirubinemia in absence of liver disease or hemolysis. This is the most common disorder associated with bilirubin metabolism with autosomal recessive inheritance. It usually precipitates during episodes of dehydration, fasting or stress like intercurrent illnesses. Here, we are reporting a case of Gilbert syndrome in 12 yrs old boy with thalassemia trait who presented with history of persistent jaundice for last 10 months. He had disproportionately higher concentration of unconjugated bilirubin which cannot be attributed to either disorder alone. Authors considered the possibility of Gilbert syndrome after ruling out hemolytic anemia. Though genetic testing is considered to be gold standard for diagnosis of Gilbert syndrome but availability is an issue. Calorie restriction test and nicotinic acid provocation test has been used to confirm GS too. Rifampicin test, another simple test which has been described in literature though not widely used in diagnosis. It has high sensitivity and specificity too. Authors had performed rifampicin test in our index case to confirm the diagnosis of GS. Here, authors wish to highlight the patients with both GS and thalassemia trait has higher bilirubin concentrations and is more likely to be icteric than either defect alone.

Keywords: Gilbert syndrome, Hyperbilirubinemia, Rifampicin test, Thalassemia trait, Uridine diphosphate glucuronyl transferase

INTRODUCTION

Gilbert syndrome is the most common autosomal dominantly inherited disorder of bilirubin metabolism.[1] It is characterized by mild unconjugated hyperbilirubinemia, normal liver enzymes and hepatic histopathology.[2] It is resulted from reduced activity of the enzyme uridine diphosphate-glucuronyl transferase which is required for glucuronidation process. The clinical diagnosis of GS in considered in presence of unconjugated hyperbilirubinemia in two occasions 6 months apart in absence of any hemolytic anemia. Gilbert originally described it in patients with total bilirubin of more than 1 mg/dl (17 µmol/L) whereas Royal college of pathologist of Australasia considered a cut off of 20 µmol/l. GS usually presents with intermittent jaundice. Other nonspecific presentations are abdominal pain, epigastric fullness, fatigue, and fat intolerance. It usually precipitates by dehydration, fasting, stress, intercurrent illnesses or vigorous exercise. The diagnosis of GS is confirmed by molecular testing. In absence of molecular testing, simple testing of bilirubin after overnight fasting or after administration of rifampicin are used to diagnose. No specific treatment is needed after diagnosis as it is a benign condition and require reassurance. Rarely, it may occur in association with some primary hematological disorder like β-thalassemia minor (thalassemia trait), glucose-6-phosphate dehydrogenase (G-6 PD) deficiency

and hereditary spherocytosis.[3,4] These patients can have considerably high serum bilirubin concentration.[3] Here, authors have described one such patient who presented with persistent unconjugated hyperbilirubinemia which turned out to be GS with thalassemia trait confirmed by rifampicin test.

CASE REPORT

A 12 years old boy presented with history of persistent jaundice for last 10 months in our outpatient. Jaundice was mild, intermittent. There was no history of blood transfusion. It was not associated with any history of hemetemesis, malena or any other sign of liver failure. Child had weight of 28 kg (below 3rd centile) and height of 132 cm (below 3rd centile). General physical examination revealed jaundice with pallor. On systemic examination, liver span was normal and spleen was just palpable. On investigation, child had hemoglobin (Hb) 8.8 g/dl, normal total and differential leucocyte count (TLC/DLC) and platelet count. Peripheral blood smear suggestive of markedly microcytic and hypochromic anaemia and anisopoikilocytosis with few target cells. Corrected retic count was 2.7% with Mean corpuscular volume (MCV) was 60.8 fl. Liver function tests revealed total serum bilirubin 4.80 mg/dl with unconjugated fraction 4.30 mg/dl, serum alkaline phosphatase 879 U/L and serum aminotransferases AST and ALT 25 U/L, and 12 U/L, respectively. On Hb electrophoresis, HbA2 was 5.1% with normal HbF level suggestive of thalassemia trait. Serum ferritin (60.80ng/ml) were normal. Direct and indirect Coombs tests were negative. Osmotic fragility test was negative. G6PD levels were within normal limit. Due to persistence of unconjugated hyperbilirubinemia in a child with thalassemia trait, possibility of Gilbert syndrome was considered. Child was subjected to rifampicin test. Child took 600 mg of rifampicin and blood samples were taken at 0, 2, 4 and 6 hours. Baseline total serum bilirubin was found to be 3.4 g/dl of which 1.2 g/dl was conjugated and 2.2 g/dl unconjugated type. After six hours of rifampicin administration, total serum bilirubin increased to 5.3 mg/dl of which 0.9 g/dl was conjugated and 4.4 mg/dl was unconjugated (Table 1). The increase in indirect bilirubin fraction satisfies the criteria for diagnosis of Gilbert syndrome.

Table 1: Rifampicin test.

Time	Total bilirubin (mg/dl)	Conjugated bilirubin (mg/dl)	Unconjugated bilirubin (mg/dl)
Baseline	3.4	1.2	2.2
2 hr post rifampicin	3.6	1.0	2.6
4 hr post rifampicin	4.2	0.9	3.3
6 hr post rifampicin	5.3	0.9	4.4

DISCUSSION

Gilbert syndrome (GS) is a benign recurrent condition usually presented with asymptomatic unconjugated heperbilirubinemia without any liver disease or evidence of hemolysis. It was first described by Augustine Gilbert and Pierre Lereboullet in 1901.[5] Later, Arias et al, described it as a disorder due to glucuronyl transferase deficiency in which eight patients with chronic nonhemolytic jaundice.[6]

Clinical diagnosis of GS includes demonstration of unconjugated hyperbilirubinemia in two occasions 6 months apart after overnight fasting blood samples with normal liver enzymes, alkaline phosphatase and GGT. Confirmation of diagnosis is done by identifying mutation in the promoter region of UDP-glucuronosyl transferase (UGT-1A) gene.[7] Though genetic testing is gold standard for confirmation of diagnosis but usually unavailable and expensive too.

Calorie restriction test and nicotinic acid provocation test has been described in the literature for confirmation.[8,9]

Rifampicin test, another simple bedside test has been used previously in various studies for confirmation for GS. Rifampicin induces cytochrome P450, hence competes with the excretory pathway of liver at cellular level resulting in increase in total and uncojugated bilirubin. This response is exaggerated in patients with GS where UGT levels are reduced as compared to normal individual.

An increase in total serum bilirubin by 2.4 mg/dl has 93.8% sensitive and 93% specific for diagnosis of GS whereas rise of indirect bilirubin of 1.3 mg/dl at 4 hrs has 100% sensitivity and specificity.[10]

In present index case, authors considered the possibility of GS in view of persistence of unconjugated hyperbilirubinemia for prolonged period which is unusual in thalassemia trait. Hence, we performed Rifampicin test which suggests increase in unconjugated bilirubin by 2.2 mg/dl, favoring diagnosis of GS. Here, we wish to highlight the patients with both GS and thalassemia trait has higher bilirubin concentrations and is more likely to be icteric than either defect alone.[9]

CONCLUSION

In conclusion, Gilbert 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.

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