

Gilbert Syndrome Presenting In a Young Boy, Confirmed by the Rifampin Test

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Gilbert syndrome is the most common inherited disorder of bilirubin metabolism. This autosomal recessive disease may be precipitated by dehydration, fasting, or stress due to an intercurrent febrile disease or vigorous exercise. To the best of our knowledge the patient reported here is the youngest child diagnosed with the syndrome.

Patient Description

An Arab Moslem boy, aged 6 years 10 months, was admitted to our department for the third time in 3 months because of recurrent abdominal pains and vomiting. No fever or diarrhea was reported. On his first two hospitalizations, no abnormal physical or laboratory findings were noted, and after a short course of intravenous fluid administration he was discharged home. On his third admission physical examination was unremarkable, including normal complete blood count, electrolytes, kidney and liver function tests, except for high serum unconjugated bilirubin values of 2.7 mg/dl. Unconjugated bilirubin was estimated as total bilirubin (3.2 mg/dl) minus conjugated bilirubin (0.5 mg/dl).

After a short course of intravenous fluid administration, the vomiting ceased and the abdominal pain resolved. Within less than 24 hours of admission a repeat liver blood examination revealed normal liver function tests including unconjugated bilirubin 0.8 mg/dl. Gilbert syndrome was suggested, and after 2 days of hospitalization, on recovery, a rifampin test was performed. Total serum unconjugated bilirubin concentrations were measured at baseline and 2, 3, 4, 20 and 24 hours after the administration of oral 600 mg

rifampin, showing values of 0.6, 0.6, 0.8, 0.9, 1.6 and 1.8 mg/dl, respectively. Less than 32 hours after initiation of the test, the serum bilirubin levels returned to normal (0.8 mg/dl). No other abnormal liver function values were noted. There is no known family history of liver disease or Gilbert syndrome among other members of the family, including the patient's siblings.

Comment

Gilbert syndrome is a mild and benign disorder that presents as an asymptomatic unconjugated ("indirect") hyperbilirubinemia in the absence of hemolysis and any underlying liver disease. If it does become apparent, it is usually not until adolescence, but appears more frequently in the second or third decade of life usually in association with stress such as intercurrent illness, fasting or strenuous exercise. Gilbert syndrome affects 3-7% of the population, with males predominating over females by a ratio of 2-7:1.

This disorder, the most common inherited cause of unconjugated hyperbilirubinemia, was first described by Augustine Gilbert and Pierre Lereboullet in 1901 [1]. Later, Arias [2] described a disorder in which eight patients with chronic non-hemolytic jaundice had glucuronyltransferase deficiency.

Patients may report vague abdominal discomfort, general fatigue and malaise for which no cause is found. Abdominal symptoms may be multifactorial, with underlying anxiety probably playing an important role. These episodes resolve spontaneously and no treatment is required apart from supportive care.

The genetic basis of the disease was elucidated in 1995 [3]. Decreased hepatic bilirubin uridine diphosphate glucuronyltransferase is the main pathogenic factor, though transport abnormality in hepatocytes and occult hemolysis may also contribute. In patients diagnosed with Gilbert syndrome, the hepatic bilirubin glucuronidation activity was found to be approximately 30% lower than normal.

The differential diagnosis of Gilbert syndrome from other unconjugated hyperbilirubinemic states is important when considering the further management of a patient. Other hereditary unconjugated hyperbilirubinemias include Crigler-Najjar syndrome type I and Crigler-Najjar syndrome type II, both of which are autosomal recessive with clinical expression of much more severe hyperbilirubinemia during the first days of life. Acquired unconjugated hyperbilirubinemias have also been reported in newborns. These include the Lucey-Driscoll syndrome in which an inhibitor of the UGT enzyme activity is acquired from the mother's serum and breast milk, a jaundice in which the inhibitor of enzyme activity is transmitted to the infant through lactation. In healthy individuals with no family history of Gilbert syndrome, the finding of unconjugated hyperbilirubinemia is often accidental; therefore several provocative tests including fasting and nicotinic acid were suggested for the diagnosis of the syndrome. Serum bilirubin level increases after 24 hours fasting and pro-

UGT = uridine diphosphate glucuronyltransferase

longed fasting raises the sensitivity of the test. Caloric restriction to about 400 Kcal in 24 hours raises the serum unconjugated bilirubin level twofold in affected individuals. The nicotinic acid provocation test has also been suggested for the diagnosis of the disorder. Following intravenous administration of nicotinic acid there is a significant rise in unconjugated bilirubin. However, this test is non-specific and may be positive in unconjugated hyperbilirubinemia regardless of the cause and, therefore, is probably of no value in differentiating Gilbert syndrome from other entities including chronic liver diseases.

The rifampin test was first considered as a diagnostic test for the syndrome in the Spanish medical literature, and only recently in English studies [4]. Rifampin induces cytochrome P-450 isoenzymes and competes for the excretory pathways in the liver at the cellular level. In patients with Gilbert syndrome who have reduced levels of UGT, rifampin causes an exagger-

ated elevation in unconjugated total serum bilirubin levels [5], as was confirmed in our patient.

This simple and available procedure can be performed at bedside and can confirm the diagnosis of Gilbert syndrome, which is often an accidental finding in healthy individuals and patients with unrelated diseases. Since this is a genetically transmitted disease, a carrier's family members should be warned of the possibility of serious jaundice under specific circumstances. The association between fasting and hyperbilirubinemia, particularly among fasting Moslems with the syndrome (during Ramadan), is of paramount importance. Once the diagnosis is established, the most important aspect of management is to reassure patients that the disorder is benign and inconsequential, that the prognosis regarding this syndrome is excellent, that they should avoid long fasting, and that there is no need for further unnecessary medical investigations.

References

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