

Hereditary spherocytosis coexisting with Gilbert's syndrome: a diagnostic dilemma

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ABSTRACT

Haemolytic anaemia generally gives rise to only a modest elevation of serum bilirubin. Unconjugated hyperbilirubinaemia of an extreme degree should raise suspicion of additional factors, such as Gilbert's syndrome, hepatocellular dysfunction or renal failure. We present a 17-year-old boy with hereditary spherocytosis coexisting with Gilbert's syndrome.

Keywords: Gilbert's syndrome, haemolytic anaemia, hereditary spherocytosis, unconjugated hyperbilirubinaemia

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INTRODUCTION

Gilbert's syndrome, a mild form of unconjugated hyperbilirubinaemia, is a relatively common and often incidental finding in healthy individuals and patients with unrelated diseases. The coexistence of Gilbert's syndrome with other clinically significant conditions could interfere with their diagnoses. We describe a case of hereditary spherocytosis, which, to our surprise, had extreme unconjugated hyperbilirubinaemia, posing a diagnostic dilemma. After excluding common causes of unconjugated hyperbilirubinaemia, clinical and laboratory re-evaluation revealed high-grade hyperbilirubinaemia on caloric restriction and a decrease in hyperbilirubinaemia after phenobarbitone challenge leading to the presumptive diagnosis of Gilbert's syndrome, which was confirmed on genetic analysis.

CASE REPORT

A 17-year-old boy presented with jaundice for three years. There was a history of recurrent episodes of pain, nausea and vomiting in the right hypochondrium. There was no history of alcoholism, hepatitis, drug ingestion or drug abuse. His family history revealed that his two elder siblings were also suffering from jaundice since childhood. His father was healthy, but mother also had jaundice since childhood. On clinical examination, he had icterus and modest hepatosplenomegaly. Laboratory data revealed haemoglobin level of 8 g/dL with a reticulocyte count of 4.5%. Serum bilirubin was elevated (total 12 mg/dL, unconjugated 9.5 mg/dL) with normal liver enzymes. His previous medical record showed

a persistent haemoglobin level of 7.5–8 mg/dL, and serum bilirubin of 11.5 to 12.5 mg/dL, thus excluding any haemolytic crisis in the present situation. Peripheral smear showed normocytic, normochromic red blood cells, increased polychromasia and population of spherocytes. Other tests included normal vitamin B12, folate, iron studies, rheumatoid factor, antinuclear antibodies and rapid plasma reagin test. Glucose-6-phosphate dehydrogenase test, Ham's test, Coomb's direct and indirect tests, and haemoglobin electrophoresis were also normal. Incubated osmotic fragility was increased.

Bone marrow biopsy revealed hypercellular marrow with mild erythroid hyperplasia and an M:E ratio of 1:1. Red cell enzyme assays showed increased activities of glucose phosphate isomerase, monophosphoglycerate mutase, phosphoglycerate kinase, pyruvate kinase, lactate dehydrogenase, and glutathione peroxidase. These enzyme activities are commonly found to be elevated in young erythrocytes in patients with haemolytic anaemia. Furthermore, the biochemical analysis of the red cell membrane proteins indicated a deficiency of band 3.0. This led to a conclusive diagnosis of hereditary spherocytosis. Both jaundiced siblings and their mother were evaluated and all of them had hereditary spherocytosis. Other family members were also evaluated and had normal complete blood counts, total bilirubin and peripheral smears. Abdominal ultrasonography was suggestive of cholelithiasis with splenomegaly with normal common hepatic duct diameter, which was confirmed on magnetic resonance cholangiopancreatography.

To our surprise, the patient continued to have extreme unconjugated hyperbilirubinaemia on repeated serum bilirubin examinations, even though haemolytic anaemia rarely causes a rise in the serum bilirubin above 5 mg/dL. Subsequently, causes of unconjugated hyperbilirubinaemia, such as drug intake or liver disease, were excluded. Finally, the diagnosis of Gilbert's syndrome was made. Clinical and laboratory re-evaluation showed high-grade hyperbilirubinaemia on caloric restriction (Table I), and reduction in bilirubin levels after phenobarbitone intake (Table II). Genetic analysis using polymerase chain reaction and electrophoresis in a polyacrylamide gel revealed the (TA)⁷ / (TA)⁷ genotype described in patients with Gilbert's syndrome, thus confirming the diagnosis. He underwent elective cholecystectomy and splenectomy. Postoperative total

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Table I. Effect of caloric restriction on various laboratory tests.

Biochemical parameter	Pre-caloric restriction	Post-caloric restriction
Serum bilirubin (unconjugated) (0.2–0.8 mg/L)	9.5	20.4
Serum LDH (94–172 units/L)	140	142
Reticulocyte count (0.5%–1.5%)	4.5	4.8

Table II. Effect of phenobarbitone on various laboratory tests.

Biochemical parameter	Pre-phenobarbitone therapy	Post-phenobarbitone therapy
Serum bilirubin (unconjugated) (0.2–0.8 mg/L)	9.8	4.6
Serum LDH (94–172 units/L)	142	144
Reticulocyte count (0.5%–1.5%)	4.9	4.8

serum bilirubin was 1.5 mg/dL with unconjugated bilirubin of 1.0 mg/dL. He did well postoperatively, and did not experience any complications at six months follow-up. The mild postoperative hyperbilirubinaemia resulting from Gilbert's syndrome was also explained to him.

DISCUSSION

Hereditary spherocytosis is an inherited disorder characterised by intrinsic defects in the red cell membrane that render red cells spheroid, less deformable, and vulnerable to splenic sequestration and destruction. The prevalence of hereditary spherocytosis is highest in Northern Europe, where rates of one in 5,000 have been reported. An autosomal dominant inheritance pattern is seen in 75% of cases. The underlying primary molecular abnormality is heterogeneous; it may affect several membrane proteins including spectrin, ankyrin, band 3 and rarely, protein 4.2.⁽¹⁾ Most patients have icterus and cholelithiasis due to chronic haemolysis. Gilbert and Lereboullet first described the Gilbert's syndrome in 1901 as "La cholemie simple familiale".⁽²⁾ It is the most common inherited disorder of bilirubin metabolism. It is characterised by mild, chronic, fluctuating increase in serum unconjugated bilirubin levels in the absence of bilirubinuria or symptoms and signs of liver disease. It is estimated that between 2% and 5% of the general population have Gilbert's syndrome, as determined by elevated indirect serum bilirubin levels. Males are more frequently affected than females. Gilbert's syndrome is often diagnosed around puberty, which may be related to an increased haemoglobin turnover and possibly, the inhibition of bilirubin glucuronidation by endogenous steroid hormones.⁽³⁾ Moreover, the mean bilirubin concentration in Gilbert's syndrome is significantly higher in males.⁽⁴⁾ Patients with Gilbert's syndrome have a deficiency in hepatic bilirubin glucuronidation – about 30% of normal activity.⁽⁵⁾ The bile contains more bilirubin

monoglucuronide than diglucuronide. The genetic basis of this disorder has been clarified by the discovery that the promoter region (A(TA)₆TAA) of the gene encoding UGT1*1 has an additional TA dinucleotide, resulting in a change to (A(TA)₇TAA).^(6,7)

Patients with simultaneous presence of hereditary spherocytosis with Gilbert's syndrome have bilirubin levels higher than those with either abnormality. The possibility of Gilbert's syndrome should be considered in a case of haemolytic anaemia with extreme unconjugated hyperbilirubinaemia. It appears unlikely that there is any causal relationship between hereditary spherocytosis and Gilbert's syndrome and likely to be a mere coincidental finding. But, it is clinically important because coexistence increases the risk of gallstone formation as well as the incidence of haemolytic crisis. It is also important to prognosticate the patient with a simultaneous presence of hereditary spherocytosis and Gilbert's syndrome about postsplenectomy unconjugated hyperbilirubinaemia, which will not warrant any treatment.

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