CASE REPORT

Gilbert's Syndrome after Ritualistic Prolonged Fasting of *Chhath Puja* in Bihar, India: A Case Report and Literature Review

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Abstract

Gilbert' syndrome (GS), most common hereditary cause of unconjugated hyperbilirubinemia due to polymorphisms in uridine diphosphate glucuronosyltransferase (UGT) enzyme, was first described by Augustin Nicolas Gilbert and Pierre Lereboullet in 1901. It becomes apparent around adolescence and often precipitated by prolonged fasting, intercurrent illness, or strenuous exercise. Gilbert's syndrome has an excellent prognosis and does not require any treatment. But recent studies have shown that patients with GS are more susceptible to enhanced toxicity of several drugs using UGT enzyme in their metabolism. Also, hyperbilirubinemia is protective due to its anti-inflammatory, anti-oxidant, and anti-cancer properties, particularly in colon cancer. In India, followers of different religious practice a ritualistic prolonged fastings, which can predispose susceptible cases of GS to unconjugated hyperbilirubinemia. We report a rare case of GS unmasked by ritualistic prolonged fasting of *Chhath Puja* in Bihar to increase awareness about it among medical fraternity and patients.

Keywords: Bilirubin, Gilbert's syndrome, Hemolysis, Hyperbilirubinemia.

Indian Journal of Medical Biochemistry (2019): 10.5005/jp-journals-10054-0127

Introduction

In 1901, Gilbert's syndrome (GS) was first described by Augustin Nicolas Gilbert and Pierre Lereboullet as benign, familial, fluctuating, mild, and unconjugated hyperbilirubinemia without underlying hemolysis and with normal routine tests of liver function and liver histopathology and named it as "La cholemie simple familiale."[1,2] Subsequently, it was further elaborated by Meulengracht in 1946 and Arias et al. in 1962. Gilbert's syndrome is the most common inherited cause of unconjugated hyperbilirubinemia, others being Crijlar–Najar syndrome I (CN I) and Crijlar–Najar syndrome II (CN II). Gilbert's syndrome affects 3–10% of the Caucasians population with men predominating over women by a ratio of 2–7:1 and inherited as both autosomal dominant and autosomal recessive traits.[1] Although most cases of GS remain asymptomatic throughout life, severe jaundice can be precipitated by dehydration, prolonged fasting, stress, vigorous exercise, or any intercurrent febrile illness. Patients usually complain of vague abdominal discomfort, malaise, and generalized weakness, which are resolved spontaneously with reassurance and supportive care without any treatment.[2] Since the time it was first described, GS was considered a benign clinical entity without any morbidity and mortality and excellent prognosis. However recently, many studies have proposed that affected individuals may be more prone to develop liver injury following treatment with various drugs, such as paracetamol, propofol, irinotecan, indinavir, and xenobiotics. Also, the genetic defect in GS patients may adversely influence the outcome of liver transplantation.[3–5] Also, hyperbilirubinemia may be protective due to its potent anti-inflammatory, anti-oxidant, and anticancer properties, especially in colon carcinoma.[1,3,6] In India, followers of different religions practice a ritualistic fastings for prolonged periods and may lead to unmasking of GS, exacerbate jaundice and related complications in GS patients. We report a rare case of GS developing after ritualistic prolonged fasting of *Chhath Puja* in Bihar to increase awareness about this rare benign entity among medical fraternity and patients.

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How to cite this article: Sharma HK, Prashar S. Gilbert's Syndrome after Ritualistic Prolonged Fasting of *Chhath Puja* in Bihar, India: A Case Report and Literature Review. Indian J Med Biochem 2019;23(3): 354–356.

Source of support: Nil

Conflict of interest: None

Case Description

A 28-year-old women patient hailing from rural Bihar reported complaints of yellowish discoloration of eyes, recurrent abdominal pains, nausea, and generalized weakness. There was no history of fever, diarrhea, or any other contributory illness. She gave history of keeping ritualistic *Chhath Puja* fast for 2 days just before her symptoms started. She had similar symptoms earlier whenever she kept regular religious fast for shorter duration but her symptoms were mild and she did not take any treatment. On examination, she had bilateral icterus without hepatosplenomegaly. Her routine hematological laboratory tests revealed normal hemoglobin, total and differential leukocyte counts, and platelet counts. Peripheral blood smear examination revealed normocytic normochromic red blood cells (RBCs) without any evidence of hemolysis. Reticulocyte count was 0.8% (normal range 0.2–2%). Liver function tests including serum alanine aminotransferase and aspartate aminotransferase values were all within normal limits except mild unconjugated hyperbilirubinemia (total and indirect serum bilirubin 3.2 mg/dL and 2.6 mg/dL, respectively). Viral markers' studies including hepatitis B surface antigen and antihepatitis C virus were also negative. Urine examination and stool examination, chest radiograph and ultrasound abdomen were unremarkable. She was further tested

Table 1: Results of fasting test

Before fasting		
Serum bilirubin	Total—1.8 mg/dL	Indirect—1.2 mg/dL
After 48 hours of fasting		
Serum bilirubin	Total—4.4 mg/dL	Indirect—3.7 mg/dL

for red cell osmotic fragility, electrophoretic pattern of hemoglobin, and glucose-6-phosphate dehydrogenase (G-6 PD) level to rule out other inherited causes of hemolysis that were within normal limits. She did not give any long-term drug intake or substance abuse history. Based on all investigations, the possibility of GS was entertained and she was subjected to fasting or provocation test giving 400 kcal/day for 48 hours and total and indirect serum bilirubin measured (Table 1).

After 24 hours, her normal diet was resumed, which lowered serum bilirubin levels comparable to prefasting levels (total serum bilirubin 2.0 mg/dL and indirect serum bilirubin 1.5 mg/dL). Based on her symptoms, mild unconjugated hyperbilirubinemia and fasting test results, she was diagnosed as a case of GS. With supportive care, her jaundice subsided and she was discharged with instruction to avoid prolonged fasting or stress and in future, inform her doctor about this before taking any treatment.

Discussion

During breakdown of senescent erythrocytes, heme group of hemoglobin yields about 80% of bilirubin whereas remaining 20% bilirubin of the daily production is derived from heme proteins, such as the cytochrome P-450 isoenzymes, myoglobin, catalase, and peroxidase, and so on.[1,7] It is formed in the reticuloendothelial cells (monocytes and macrophages) of the spleen, bone marrow and in hepatic Kupffer cells and transported to the liver in the bound form with plasma albumin. In normal adults, approximately 250–300 mg (3.8 mg/kg) bilirubin is formed in adults per 24 hours while in neonates, due to increased breakdown of RBCs, daily production of bilirubin is very high.[1,7,8] Since unconjugated bilirubin is lipid soluble, hepatic conjugation process is essentially required for converting unconjugated bilirubin into conjugated bilirubin monoglucuronide and diglucuronide and to make unconjugated bilirubin water soluble and allow its excretion into the bile. A specific isoform of hepatic conjugating enzyme system uridine diphosphate glucuronosyltransferase (UGT), located in the endoplasmic reticulum of hepatocytes converts unconjugated bilirubin to conjugated bilirubin by attachment of two molecules of glucuronic acid to carboxyethyl groups of bilirubin.[5] Uridine diphosphate glucuronosyltransferase enzymatic activity is influenced by multifactorial causes like gender, age, thyroid hormones, and microsomal enzyme inducing agents, such as rifampicin and phenobarbital. Defective conjugation in microsomes due to various factors, such as neonatal immaturity, CN I and CN II diseases, GS, inhibition by drugs like novobiocin, atazanavir, amitriptyline, and ketoconazole; and escape form conjugation due to liver cirrhosis can lead to unconjugated hyperbilirubinemia.[7] In 1995, Bosma et al. proposed that the genetic basis of reduced hepatic bilirubin glucuronidation in GS is due to a variant TATAA element (which contains two extra nucleotides, TA) in upstream promoter region of the gene for bilirubin UGT located on chromosome 2. These two extra TA nucleotides resulted in homozygous polymorphism in the promoter region of the gene encoding bilirubin *UGT1A1* gene—A(TA)6TAA to UGT1A1 gene—A(TA)7TAA and presence of this insertion recently named as UGT1A1*28.[1,8] The TATAA element being the binding site for transcription factor IID, has an important role in the initiation of transcription and presence of the longer TATAA element in patients with GS results in the reduced expression of a reporter gene leading to higher mean serum bilirubin levels in normal and healthy subjects and reduced accuracy of transcription initiation.[1,7,8] Although reduced expression of bilirubin UGTA1G1 is essential for the syndrome, usually it is not sufficient for the complete manifestation of the phenotype. In addition to reduced glucuronidation, presence of other inherited or acquired factors affecting bilirubin metabolism like fasting, intercurrent illness or stress, impaired hepatic uptake, and hemolysis due to other inherited causes like hereditary spherocytosis, G-6 PD deficiency, and thalassemia trait may result in the full manifestation of the syndrome.[1,7,9] Another observation revealed that compared with women, men who were homozygous for the longer TATAA element had significant elevations in their serum bilirubin levels, probably due to a greater bilirubin load in men per kilogram of body weight or the down-regulation of UGT activity by testosterone.[1,7,8] In a study conducted by Farheen et al. on high frequency of (TA)7TAA allele in India and its interaction with novel trinucleotide CAT insertion in promoter of the gene for bilirubin UGTA1G1, genetic heterogeneity and clinical overlap of all three syndromes of inherited unconjugated hyperbilirubinemia namely GS, CN I, and CN II syndromes were seen.[4] Their study also elaborated that these syndromes may not be mutually exclusive clinical-genetic entities but are different windows of the quantitative spectrum of elevated serum unconjugated bilirubin levels. In India, association between homozygosity for the (TA)7TAA allele and GS is much stronger (80%) compared with earlier reported incidence from most other ethnic groups.[4] Homozygous GS patients shows graded reduction of UGT1 activity with increasing length of the TA repeats and progressively increasing serum unconjugated bilirubin levels as demonstrated by having, respectively, a 52% (in 7/7 homozygotes) and a 37% reduction (in 7/6 heterozygotes) of UDP glucuronyl transferase activity in liver tissue homogenates.[4,5] Though the insertion of additional TA repeats in the (TA)6TAA promoter sequence of the *UGT1A1* gene is the most common variation associated with GS, (TA)5, and (TA)8 sequences in the TATAA box have also been found.[4] Population studies have revealed considerable genetic heterogeneity of UGT1A1*28 allele among different populations having other mutations like G71R and the Y486D responsible for enhanced serum bilirubin levels in subsets with low frequency of the UGT1A1*28 allele.[1] Patients with GS have a deficiency in bilirubin UGT activity about 30% of normal.[1,4,8] Most cases of GS are usually diagnosed around puberty with male preponderance, possibly due to an inhibitory effect of testosterone and an enhancing effect of estroprogestogens on the activity of UGT.[7,8] Cases with GS are usually diagnosed incidentally during routine blood tests or when hyperbilirubinemia gets aggravated by an intercurrent illness, stress, prolonged fasting, or dehydration. Patients usually reports with vague symptoms of malaise, nausea, recurrent vomiting, and abdominal discomfort over liver without any evidence of hepatomegaly or any other systemic abnormality.[2] On exanimation, jaundice is mild, intermittent with serum bilirubin levels <6 mg/dL. However, in one-third of cases, serum bilirubin level may be normal to <3 mg/dL.[5] In the absence of any other underlying systemic disease, GS cases can be easily diagnosed in majority of the cases by triad of raised bilirubin level that is predominantly unconjugated with normal liver enzymes and no evidence of hemolysis.[2] Occasionally, additional diagnostic tests are required to confirm the diagnosis of GS and include fasting or calorie restriction for

48 hours, administration of microsomal enzyme inducers, such as rifampicin and phenobarbitone, and intravenous nicotinic acid, thin-layer chromatography, polymerase chain reaction, and very rarely, liver biopsy.[2] Most commonly performed test is fasting test, also known as caloric restriction or starving test, originally proposed by Augustine Gilbert itself in which caloric restriction to about 400 kcal in 48 hours raises the serum unconjugated bilirubin level two-fold in patients which becomes normal after 24 hours of resuming normal diet.[2,5,10] In a study by Kotal et al., mechanism behind fasting-induced hyperbilirubinemia was studied in Gunn rat models as Gunn rats have inherited absence of UGT. Their study revealed that the fasting results in reduced intestinal motility leading to decreased elimination of bile pigments and causing their enhanced enterohepatic circulation and increased reflux of bilirubin in plasma.[11] Although fasting test is also positive in patients with hemolysis, obstructive jaundice, alcoholic cirrhosis, chronic active hepatitis, and other liver diseases, magnitude of the rise is less than that observed with GS. Rifampicin, a potent cytochrome P-450 isoenzyme inducer agent helps in diagnosis of GS by inducing cytochrome P-450 isoenzymes and competing for the excretory pathways in the liver at the cellular level resulting in exaggerated elevation in total serum bilirubin levels. Absolute increase of bilirubin to >1.9 mg/dL, 2–6 hours after the administration of 900 mg of rifampicin distinguishes patients with GS from those without it. Usually, apart from fasting test, no other tests are required to make diagnosis of GS.[1,2,4] Although GS is hereditary, family history is usually not considered important for diagnostic work-up because positive family history was reported in less than 4% of patients, 27–55% of siblings, and 16–26% of parents.[1,4] In fact, most of the times, patients are diagnosed to have GS without any invasive and unnecessary testing.[10] Gilbert's syndrome has an excellent prognosis and require only reassurance and explanation to the patients without any pharmacological treatment. Hyperbilirubinemia is lifelong and not associated with increased morbidity and mortality.[5] Hereditary hemolytic diseases, such as hereditary spherocytosis, and thalassemia are also frequently associated with GS and rise of unconjugated hyperbilirubinemia in these disorders depends on their frequent mutual association.[9] Although hyperbilirubinemia can be detrimental especially in neonates, recently various studies have demonstrated the protective effects of mild hyperbilirubinemia due to its strong anti-inflammatory and antioxidant activity.[3,6] Recent study conducted by Jiraskova et al. revealed that while hyperbilirubinemia in neonatal brain under specific pathologic conditions is responsible for oxidative stress and neurotoxicity, bilirubin has been increasingly recognized as a potent endogenous antioxidant when only mildly elevated mild unconjugated hyperbilirubinemia has also been demonstrated to have anti-cancer properties. Low serum bilirubin levels are associated with an increased risk of colorectal carcinoma (CRC) in both genders and each 1 mol/L decrease in serum bilirubin was associated with a 7% increase of CRC risk.[3] Various studies on Gunn rats model proposed that the lower incidence of aging-associated pathologies such as coronary heart disease, atherosclerosis, cancer, and diabetes in subjects with mild elevation of serum bilirubin might be due to their resistance to aging associated inflammation and metabolic deterioration, driven by attenuated oxidative signaling.[1,3,6]

Clinical Significance

Gilbert's syndrome should be suspected if the patient has a mild unconjugated hyperbilirubinemia with normal liver function tests, no overt signs of hemolysis, and without any underlying disease. But in presence of hemolysis, other hereditary causes of hemolysis should be sought. Awareness about appearance of jaundice after prolonged fasting, intercurrent illness, or repeated vomiting should be stressed upon on all patients with GS. It is also is very pertinent for patients to inform their treating physician to avoid drugs which metabolize by hepatic glucoronidation like paracetamol, propofol, irinotecan, indinavir, and xenobiotics to avoid harmful effects of altered metabolism and enhanced toxicity.

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