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# Facing the Odds: A Teen's Struggle with Chronic Hyperbilirubinemia and Frequent Rejections in State & National Sports Competitions

**Dr. Heti Mistry[1], Rudra Pankajkumar Trivedi[2], Aditya Jain[3], Dhvani Pankajkumar Trivedi[4]**

[1]MD, Assistant professor, Department of Medicine, GMERS Medical College, Vadodara, Gujarat

[2]MBBS, GMERS Medical College, Vadodara, Gujarat

[3]MBBS, GMERS Medical College, Vadodara, Gujarat

[4]MBBS, GMERS Medical College, Vadodara, Gujarat)

**Abstract:** ***This case report presents a comprehensive overview of a case involving a 15 years old male patient with Gilbert syndrome and a history of undiagnosed intermittent unconjugated hyperbilirubinemia; who was often asymptomatic or sometimes experience episodes of mild jaundice, which worsens during intercurrent illness or stress. Jaundice is usually manifested as yellowish discoloration of the skin and sclera due to unconjugated bilirubin levels. The patient had no other complaints. [1] Extensive investigations, including blood tests, imaging studies revealed increased indirect and direct bilirubin level with absence of hepatocellular disease or any other abnormality in liver or spleen. The consistent elevated levels of bilirubin levels may direct us towards GS but it is also very important to exclude the other similar syndromes. Differential diagnosis of GS involves excluding other inherited and acquired conditions that manifest with similar clinical features such Criggler - Najar syndrome (type 1 and 2), Dubin Johnson syndrome (ABCC2), and hepatic conditions like Wilson's disease (ATP7B) and Rotor syndrome (SLCO1B1 and SLCO1B3). [2]Molecular diagnosis was very essential for distinguishing Gilbert syndrome from other hepatic disorders presenting with unconjugated hyperbilirubinemia. Molecular diagnosis was done with UGT1A1 Gene Polymorphism (Nucleotide TA Repeat) and Fragment Analysis; and the result showed 7/7 TA repeats [Genotype Nomenclature – UGT1A1*28/28] which demonstrates Reduced Glucuronidation activity with significant risk for grade 4 neutropenia or severe diarrhea following Irinotecan treatment. By the confirmation of this syndrome, we get to know that the Molecular basis of each syndrome facilitates accurate diagnosis and appropriate management. [3]***

**Keywords:** Gilbert Syndrome, Unconjugated Hyperbilirubinemia, Gene mutation

## 1. Introduction

Gilbert syndrome is a common hereditary benign liver condition that is usually inherited as a recessive pattern but sometimes it can be an autosomal dominant condition characterized by elevated indirect hyperbilirubinemia in the absence of hepatocellular disease. In Gilbert syndrome, uridine diphosphate - glucuronyl transferase activity is reduced to 30% of the normal, resulting in indirect hyperbilirubinemia. [4] In its typical form, hyperbilirubinemia is noticed in Adolescents. However, Gilbert syndrome in combination with other prevailing conditions such as breastfeeding, G - 6 - PD deficiency, thalassemia or cystic fibrosis may prolong or potentiate severe hyperbilirubinemia. [5]

## 2. Case Presentation

A 15 - year - old male boy repeatedly facing rejections at state and national level sports competitions. Chronic hyperbilirubinemia was noticed on reports, which was often asymptomatic and he also reported to have experienced episodes of mild jaundice. [6] Notably, such chronic hyperbilirubinemia was not present in either the patient's mother or father. Further, on physical examination revealed clinical signs of pallor & icterus. The patient went through multiple investigations like CBC, CRP, Echocardiography, USG Abdomen, Sickling test, HPLC and LDH. But no distinguishing abnormality was noted, except elevated bilirubin levels.

Further no other signs of liver disease, hemolysis or any other Neuropsychiatric problems were seen. Also, Wilson disease was ruled out by no Kayser - Fleischer Ring was seen around the iris and 24 hours urinary Copper level test was also normal. [7] And similarly other diseases like Criggler Najar syndrome, Rotor syndrome were ruled out by genetic studies. [8] After 3 - 4 months of investigations, the diagnosis of Gilbert syndrome was suspected and confirmed by Molecular/Genetic studies (i. e. PCR and TA repeats). [9]

## 3. Investigations and Findings

Laboratory investigations revealed an elevated bilirubin profile [direct – 0.9mg/dl, indirect – 1.9mg/dl, Total – 2.8mg/dl], absolute reticulocyte count – 82.24% and Genetic Studies [PCR & Fragment Analysis] showed 7/7 TA repeats [Genotype Nomenclature – UGT1A1*28/28]. Liver function tests, CBC, PT INR, ap51 tests were Normal, DCT - KT was negative and no other signs of liver disease were present; Further, Patterns by HPLC were done showing [Hb A0 - 84.30%, Hb A2 - 3.30%, Hb F - 0.8%] and LDH - 198U/L all of which is within the normal range.

**Management & Outcome**:
The gastroenterologist suspected the diagnosis of Gilbert syndrome, given the characteristic association with constant

increased bilirubin profile with no other abnormality seen in Ultrasound sonography of the abdomen. [10] No specific treatment was done for this and was only advised to avoid stress and fasting that may aggravate jaundice.

## 4. Discussion

Gilbert syndrome (GS) is a common hereditary condition characterized by intermittent jaundice due to unconjugated hyperbilirubinemia in the absence of liver disease or hemolysis. It is an autosomal recessive disorder caused by a mutation in the UGT1A1 gene, which results in reduced activity of the enzyme UGT1A1. This enzyme is responsible for the conjugation of bilirubin, facilitating its excretion. [11]

In this case, we presented a 15 - year - old Indian male diagnosed with Gilbert syndrome. His serum bilirubin levels were elevated, primarily due to unconjugated bilirubin, which is consistent with GS.

GS is prevalent worldwide, with varying incidence rates across different ethnicities. It affects approximately 4 - 16% of the population. [4] The condition often remains underdiagnosed due to its benign nature and the mildness of symptoms.

The genetic basis of GS involves mutations in the promoter region of the UGT1A1 gene located on the long arm (q) of chromosome 2 (2q37). [12] This mutation reduces the transcription of the UGT1A1 enzyme, leading to decreased bilirubin conjugation. The most common mutation associated with GS is the UGT1A1*28 allele. This involves the insertion of two extra bases (TA) in the TATAA element of the gene's promoter region:

Normal: A (TA) 6TAAGS Mutation: A (TA) 7TAA [13]

This mutation reduces UGT1A1 enzyme production, leading to decreased bilirubin conjugation and subsequent hyperbilirubinemia.

Patients with GS typically present with mild jaundice that may be exacerbated by physical stress, fasting, illness, or exertion. Symptoms are often more noticeable during puberty, as in our patient, due to hormonal changes, as well as excess physical activity affecting bilirubin metabolism. Aside from jaundice, patients are usually asymptomatic and do not exhibit signs of liver disease. [14]

The diagnosis of GS is primarily clinical, supported by laboratory tests. However, in this case it was primarily built on laboratory findings. Key diagnostic criteria include:

- Elevated serum unconjugated bilirubin.
- Normal SGPT, SGOT, ALP, GGT (Liver enzymes) and LDH levels. [15]
- Genetic testing can confirm the presence of UGT1A1 mutations [16]

**Genetic Testing Methods**

Several methods can be employed for molecular diagnosis of GS:

1) PCR - RFLP (Polymerase Chain Reaction - Restriction Fragment Length Polymorphism): This technique amplifies the UGT1A1 promoter region and uses restriction enzymes to detect the presence of the extra TA repeat. [17]
2) DNA Sequencing: Direct sequencing of the UGT1A1 gene can identify the specific mutation and potentially reveal other rare variants.

In our patient, PCR - FLP rendered positive results, thus confirming the diagnosis of Gilbert's syndrome.

GS is a benign condition that does not require treatment. Patients should be reassured about the benign nature of the disorder. Though this condition does not carry significant morbidity, the significance of diagnosis lies in the intrinsic and extrinsic triggers that may exacerbate the hyperbilirubinemia and lead to more serious problems. [4] One of the main triggers being drugs. [18]

**Drug Metabolism in GS:**

Patients with GS have reduced UGT1A1 enzyme activity, which not only affects bilirubin conjugation but also the metabolism of certain drugs. This can lead to:

- Increased drug toxicity
- Prolonged drug effects
- Potential drug - induced hyperbilirubinemia

**Specific Drugs and Drug Classes to Avoid or Use with Caution:**

1) Irinotecan: This chemotherapy drug is metabolized by UGT1A1. GS patients are at higher risk of severe side effects, including neutropenia and diarrhea.
2) Acetaminophen (Paracetamol): High doses should be avoided as GS patients may have reduced glucuronidation capacity. This especially applies for Indian populations, where such extensive consumption of this OTC drugs persists since the advent of COVID 19
3) Atazanavir: This HIV protease inhibitor can cause significant hyperbilirubinemia in GS patients.
4) Gemfibrozil: This lipid - lowering drug competes with bilirubin for UGT1A1 binding sites.
5) Nilotinib: A tyrosine kinase inhibitor that can increase unconjugated bilirubin levels. [19]

Patients with Gilbert syndrome have an increased incidence of gallstones. [20]

It is essential to educate patients and their families about the condition, potential triggers for jaundice, and the importance of avoiding unnecessary investigations and treatments.

The prognosis for GS is excellent, with patients having a normal life expectancy and no increased risk of liver disease. However, awareness of the condition is crucial to prevent misdiagnosis and unnecessary anxiety.

## 5. Conclusion

This case underscores the diagnostic challenges associated with gilbert syndrome due to its rarity and minimal clinical signs and symptoms. It highlights the importance of recognizing Gilbert syndrome, especially in adolescents presenting with asymptomatic hyperbilirubinemia.

Awareness and understanding of the condition can prevent unnecessary diagnostic procedures and provide reassurance to patients and their families. Further studies on the genetic variations and prevalence of GS in different populations, including the Indian population, could provide more insights into this common but often under diagnosed condition.

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