GILBERT'S SYNDROME: ETIOLOGY, CLINICAL MANIFESTATIONS AND DIAGNOSTIC APPROACHES

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Abstract. Gilbert's Syndrome (GS) is a common, benign hereditary disorder of bilirubin metabolism characterized by intermittent, mild unconjugated hyperbilirubinemia in the absence of liver disease or hemolysis. This review discusses the etiology, pathophysiology, clinical features, and diagnostic criteria of GS. Recent genetic findings, particularly the role of polymorphisms in the UGT1A1 gene, are examined. Despite being clinically insignificant in most cases, GS has implications for drug metabolism and differential diagnosis in jaundiced patients. Understanding its benign course helps avoid unnecessary interventions and misdiagnosis.

Keywords: Gilbert's syndrome, hyperbilirubinemia, UGT1A1, jaundice, hereditary disorders, bilirubin metabolism.

Introduction. Gilbert's Syndrome (GS) is an autosomal recessive condition with reduced activity of the enzyme uridine diphosphate-glucuronosyltransferase 1A1 (UGT1A1), resulting in impaired conjugation of bilirubin [1]. It affects approximately 3–10% of the population globally, with higher prevalence in males. Often detected incidentally during routine blood tests, GS is generally considered benign but requires careful differentiation from more serious hepatic or hematological disorders [2].

Etiology and Pathophysiology. The root cause of GS lies in a genetic mutation —most commonly, an insertion of TA in the TATAA box of the UGT1A1 promoter region (UGT1A1*28 variant). This leads to reduced transcription and activity of the UGT1A1 enzyme, which is essential for conjugating bilirubin in hepatocytes [3].

Unconjugated bilirubin, being lipid-soluble, accumulates in the blood when the conjugation process is inefficient. However, other liver functions remain normal. Triggers for hyperbilirubinemia episodes include fasting, stress, illness, menstruation, and physical exertion [4,8].

Clinical Manifestations. Most individuals with GS remain asymptomatic. The hallmark clinical feature is intermittent jaundice, particularly scleral icterus, without hepatosplenomegaly or signs of chronic liver disease. Fatigue, mild abdominal discomfort, and malaise have been occasionally reported but are nonspecific and not always attributable to GS [5,10].

Importantly, GS can influence drug metabolism. Reduced UGT1A1 activity may impair clearance of drugs like irinotecan, leading to toxicities. This has pharmacogenomic implications and supports the consideration of genetic testing before initiating such therapies [6,10].

Diagnostic Approaches. Diagnosis of GS is primarily clinical, supported by laboratory findings:

Persistently elevated unconjugated bilirubin levels, typically <6 mg/dL.

Normal liver enzymes (ALT, AST), complete blood count, and hemolysis markers.

A bilirubin fasting test may provoke a rise in bilirubin, confirming diagnosis.

Genetic testing for UGT1A1 variants confirms the diagnosis but is not routinely required [1, 4].

Differential diagnosis should exclude hemolytic anemias, hepatitis, Crigler–Najjar syndrome, and drug-induced liver injury.

Management and Prognosis. GS requires no treatment, as it does not lead to liver damage or long-term complications. Patient education is key to prevent anxiety and avoid unnecessary investigations. In rare situations where bilirubin rises significantly (e.g., during illness), reassurance is sufficient.

However, pharmacovigilance is needed when prescribing UGT1A1-metabolized drugs. Lifestyle modifications, including adequate hydration and avoidance of fasting, help minimize hyperbilirubinemia episodes [2, 6,9].

Conclusion. Gilbert's Syndrome is a benign metabolic disorder that is often overinvestigated due to jaundice. A clear understanding of its genetic basis, benign course, and minimal clinical significance helps in accurate diagnosis and avoids overtreatment. Awareness of its pharmacogenetic impact is growing, especially in oncology and hepatology.

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