

# Advances in Laboratory Diagnosis and Clinical Management of Gilbert Disease: A Comprehensive Review

Nkiruka R Ukibe<sup>1</sup>, Chioma Theresa Onwe<sup>1</sup>, C.E. Onah<sup>1</sup> Ezinne G. Ukibe<sup>2</sup>, Blessing C. Ukibe<sup>2</sup>, Victory Ezennia Ukibe<sup>3</sup> and \*Emmanuel Ifeanyi Obeagu<sup>4</sup>

<sup>1</sup>Department of Medical Laboratory Science, College of Health Sciences, Nnamdi Azikiwe University, Awka, P. M. B 5025, Anambra State, Nigeria.

<sup>2</sup>Department of Medicine, College of Health Sciences, Nnamdi Azikiwe University, Awka, P. M. B 5025, Anambra State, Nigeria.

<sup>3</sup>Department of Radiography and Radiological Sciences, Nnamdi Azikiwe University, Awka, P. M. B 5025, Anambra State, Nigeria.

<sup>4</sup>Department of Medical Laboratory Science, Kampala International University, Uganda.

\*Corresponding author: Emmanuel Ifeanyi Obeagu, Department of Medical Laboratory Science, Kampala International University, Uganda, [emmanuelobeagu@yahoo.com](mailto:emmanuelobeagu@yahoo.com), ORCID: 0000-0002-4538-0161

## ABSTRACT

Gilbert's syndrome (GS) is an extensively mild condition characterized by periods of elevated levels of bilirubin in the blood. The bilirubin is an orange yellowish tinted molecule which is produced when red blood cells are broken down and this substance is eliminated from the body only after it undergoes bio-transformation in the liver which converts unconjugated bilirubin to conjugated bilirubin. When the level of unconjugated bilirubin increases beyond a determined point, the bilirubin pigment starts to discolour the cornea of the eyes (making them to appear light yellow) and with higher levels the skin may also turn to yellow (jaundice). Gilbert's syndrome also known as constitutional hepatic dysfunction and familial non haemolytic jaundice. People with Gilbert's syndrome have an inherited abnormality that causes reduced production of an enzyme involved in processing of bilirubin. A presumptive diagnosis of Gilbert's syndrome is made when unconjugated hyperbilirubinemia is noted on several occasions.

**Keywords:** Gilbert's syndrome, bilirubin, jaundice.

## INTRODUCTION

Gilbert's syndrome (GS) is a genetic benign condition involving recurrent episodes of jaundice. It is caused by high levels of a pigmented compound called bilirubin especially elevated levels of unconjugated bilirubin resulting in unconjugated hyperbilirubinemia in the setting of non-appearance of liver disease or hemolysis. The pattern of inheritance of GS is often autosomal dominant, but it can be autosomal recessive as well, depending on the type of mutation; however, patients with GS might be at a higher risk of advancement of jaundice when present in combination with haemolytic disorders, such as glucose-6-phosphate-dehydrogenase (G6PD) deficiency, ABO incompatibility, hemoglobinopathies. Patients with GS usually will have normal liver enzyme values, and normal liver synthetic functions such as albumin, and clotting factors with a negative hemolysis screening [1]. Mutations in dinucleotide

TA repeats which are existing in the promoter region of the UGT1A1 gene have been previously reported to be associated with mild unconjugated hyperbilirubinemia. GS should be differentiated from other disorders of unconjugated hyperbilirubinemia. Any alternative disease must also be taken into consideration while assessing the patient with unconjugated hyperbilirubinemia, including disorders of hepatic uptake, excretion, storage, overproduction, and conjugation. Most patients having GS are asymptomatic in nature but may express it when triggered. And these triggering factors include fasting, exercise, dehydration, and menstruation [2]. On investigation, a patient with GS may have mild jaundiced sclera and signs of triggering factors such as dehydration or intercurrent (viral) infection. The patient should not be showing signs of hepatosplenomegaly or chronic liver disease.

GS is a benign disorder that does not impact the life expectancy or will not progress to chronic disease. Higher bilirubin may shield against a range of age-

related diseases due to its effective antioxidant/anti-inflammatory properties [1, 3-6].

### EPIDEMIOLOGY OF GILBERT'S DISEASE

Gilbert syndrome has a prevalence rate between 4 and 16%. Clinical manifestations are characteristically present during early adolescence and are more frequently found in males most likely, differences in sex steroid concentrations and higher bilirubin production in males account for higher prevalence rates. Most cases are diagnosed around puberty due to higher hemoglobin turnover and

endogenous steroid hormone-induced inhibition of bilirubin glucuronidation. The frequency of the variant promoter (to be described below) is 30% among whites and blacks; the promoter mutation is less frequent in patients from Japan [1]. Patients with Gilbert syndrome and glucose-6-phosphatase deficiency are susceptible to prolonged neonatal jaundice [7-14].

### ETIOLOGY

Gilbert's syndrome typically appears to affect first in adolescence. It affects males more than females; it is due to the fact that the difference in sex steroid concentration and higher bilirubin production in the male sex which accounts for its higher prevalence. Certain trigger factor is present in patients with unconjugated hyperbilirubinemia and jaundice having Gilbert's syndrome, those being, fasting, certain illness-causing fibril, hemolytic reactions, menstruation, and physical exertion, dehydration, lack of sleep, stress, alcohol intake are the common precipitants [15]. Similarly, a lower food intake of about 400 kcal daily can increase the amount of

bilirubin by about 2 to 3-fold in 48 hours. A similar increase can also be seen with a normal caloric diet without lipid supplementation. Eventually, the bilirubin value returns to normal within 24 to 12 hours after a normal diet. Several other theories have also been projected to explain these dietary manipulations regarding unconjugated hyperbilirubinemia; Amplified cycling of bilirubin by the enterohepatic circulation, depressed conjugation due to a decrease in UDP-glucuronic acid levels, which is a co-substrate in glucuronidation and release of bilirubin from adipose cells is another hypothesis [16].

### CLINICAL PRESENTATION

The raised unconjugated bilirubin levels are often mild, but the severity can increase in times of physiological stress, increasing sometimes three to four folds above the upper limit from normal. Fasting, lack of sleep, alcohol consumption, dehydration, surgery (general anaesthesia) and concurrent illness, fibril may all precipitate clinical episodes of jaundice. Other nonspecific symptoms such as fatigue,

abdominal pain, epigastric fullness, and fat intolerance have been rarely reported. It is considered a benign illness not requiring specific treatment or any longterm medical care. GS is a heterogeneous group of illnesses, but mild episodes of jaundice are self-limiting and naturally resolve after a few days [17-24].

### PATHOPHYSIOLOGY

Unconjugated bilirubin is a by-product of red blood cell breakdown and since this product is insoluble in this form it is transported along with a blood protein called albumin to the liver [13-22]. In the liver tissue, it is bound to uridine diphosphate (UDP)-glucuronic acid before it gets into bile as a soluble product. Bilirubin is the major metabolite of heme, which is the iron-binding tetrapyrrole ring found to be in hemoglobin, myoglobin, as well as in cytochromes. The oxidation of the heme-porphyrin ring produces a straight chain compound called biliverdin by microsomal heme-oxygenase enzyme [23-34]. Biliverdin is then further reduced to produce bilirubin by the action of biliverdin reductase, a nicotinamide adenine dinucleotide phosphate (NADPH)-dependent enzyme [19-22]. After being captured by albumin, bilirubin is transported to the smooth endoplasmic reticulum and where it becomes the substrate of the UDP-glucuronosyl-transferase 1 family of polypeptide A1 enzyme (UGT1A1). UGT1A1 enzyme catalyzes the conversion of unconjugated

bilirubin to conjugated bilirubin by esterification of the propionic acid side chains of bilirubin with glucuronic acid, which is present as uridine diphosphate-glucuronic acid. This process results in the formation of diglucuronide conjugate, which is a water-soluble conjugated molecule. Conjugated bilirubin is then transported to the bile canaliculi by a membrane ATP-dependent transporter, selected as multidrug resistance-associated protein 2 (MRP2) [18]. GS is caused by the fault in the clearance of bilirubin by the hepatic conjugation enzyme called as UDP glucuronosyltransferase, that which is determined by the gene UGT1A1. Out of the main four bilirubin metabolism genes UGT1A1 was found to be the most essential because it determines the gene that encodes for uridine diphosphate (UDP)-glucuronosyltransferase 1, which is only found to be located in the liver. The function of this UGT1A1 is to mediate the glucuronidation of bilirubin, mainly unconjugated bilirubin (indirect) progressing to its increased solubility and its elimination through bile.

Therefore, any variations in the UGT1A1 gene may reduce its activity and action leading to Unconjugated hyperbilirubinemia [20-34]. Mutations in dinucleotide TA repeats which are existing in the promoter region of the UGT1A1 gene have been previously reported to be associated with mild unconjugated hyperbilirubinemia which is Gilbert's syndrome. The most comprehensively

studied variant in the UGT1A1 gene is - 53 (TA) n promoter polymorphism, which is also identified to be the most common risk factor for the development of neonatal hyperbilirubinemia. It has been noted that as the length of TA repeats increases, there is a successive reduction of UGT1A1 activity which intern leads to an increase in the unconjugated bilirubin levels.

#### LABORATORY DIAGNOSIS

A patient with GS will be asymptomatic and certainly should be without abdominal pain, itch, pale stools, and dark urine [1]. If such symptoms are presented, then further investigations (such as abdominal ultrasound) should be considered. On investigation, a patient with GS may have mild jaundiced sclera and signs of triggering factors such as dehydration or intercurrent (viral) infection. The patient should not be showing signs of hepatosplenomegaly or chronic liver disease. GS is been diagnosed using a circulating total bilirubin concentration of >17.1 μmol/L (1 mg/dL).for the diagnosis of GS, patients should have their blood collected after an overnight fasting condition, and the result should show an elevated bilirubin concentration two folds over a period of six months and should have normal serum transaminases levels (i.e. alanine and aspartate amino transaminases) and also have normal markers for biliary damage/obstruction (gamma-glutamyl transpeptidase and alkaline phosphatase). A complete blood count (including reticulocyte count) should exclude the possibility of rising in RBC destruction/production and a blood smear can

identify any irregularities in RBC structure. Jaundice can be periodically observed in a patient having GS. The appearance of jaundice typically develops at bilirubin concentrations surpassing 40–45 mmol/L and becomes a concern for some GS individuals who may reveal concentrations up to 85 mmol/L. Although indirect bilirubin can be neurotoxic at very high concentrations (i.e. >300 mmol/L). Whereas Total bilirubin concentrations in GS are not satisfactorily raised to cause neurological symptoms. If total bilirubin concentrations of >85 mmol/L are detected, additional investigations causing hyperbilirubinemia are necessary to exclude hemolytic disease and rare conditions of bilirubin metabolism (i.e. Crigler-Najjar Syndrome type 2). In a condition where the patient returns with a total bilirubin concentration of <85 mmol/L and would like to confirm the cause of his GS can do so by genotyping. Genotyping for one of many polymorphisms in the UGT1A gene (e.g., UGT1A1\*28 variant) is available but not necessarily needed.

#### DIFFERENTIAL DIAGNOSIS

##### Unconjugated Hyperbilirubinemia

- Higher bilirubin production: extravascular and intravascular hemolysis, Wilson's disease resorbing hematoma, dyserythropoiesis.
- Compromised hepatic bilirubin uptake: heart failure, portosystemic shunts, medications.

- Weakened bilirubin conjugation: Crigler-Najjar syndrome types I and II and advanced liver disease [16].

##### Conjugated Hyperbilirubinemia

- Failure of canalicular organic anion transport: Dubin Johnson syndrome.
- Failure of sinusoidal reuptake of conjugated bilirubin: Rotor syndrome.
- Extrahepatic cholestasis: choledocholithiasis, pancreaticobiliary malignancy, primary sclerosing

- cholangitis, pancreatitis, a parasitic infection.
- Intrahepatic cholestasis: viral hepatitis, alcoholic liver disease, non-alcoholic fatty liver disease, pregnancy, parenteral nutrition, primary biliary cholangitis, drugs and toxins, sepsis, infiltrative diseases, sickle cell disease, end-stage liver disease.

#### TREATMENT AND MANAGEMENT

Unnecessary testing should be evaded. Control of potential triggers may be useful to minimize variations in unconjugated bilirubin levels. Patients with signs of hepatic decompensation, including but not limited to variceal bleeding, ascites, and hepatic encephalopathy, should be treated with concern and the patient must be referred to gastroenterologists or hepatologists for the effective treatment, and possibly liver transplant may also be considered [23-24].

Upon Positive diagnosis of GS, the clinician should reassure the patients that it is not a disease, there is no impact on life expectancy nor does it progress to chronic liver disease. Patients are cautioned regarding the progression to jaundice upon stressed condition which may last up to some days. Though jaundice is a mild condition, patients are subjected to a medical review if it progresses to severe jaundice which may show signs and symptoms such as

yellowing of stools and urine, or any co-existing condition may require further investigation. GS does not require the need of medical follow-up or monitoring. There are no specific dietary restrictions/additions for GS, and alcohol can be consumed within the discretionary limits. Patients

Patients having or had Gilbert syndrome have an excellent prognosis. Results of patients with Gilbert syndrome have a similar outcome to the general population. GS is a benign disorder and there have been certain pieces of evidence that give the patients with GS a protective effect. These beneficial effects of mild unconjugated hyperbilirubinemia include a lower incidence of atherosclerosis, endometrial cancer, Hodgkin's lymphoma, and cancer-related mortality [1]. Higher bilirubin may shield against a

Gilbert's syndrome is a mild genetic liver disease where the human body is unable to correctly process bilirubin resulting in high levels of unconjugated bilirubin that might not get eliminated due to the defect in hepatic enzymes required for its elimination that lead to the yellowing of the skin, mucus membrane, nails, and sclera of eyes. GS is a benign disorder that does not impact the life expectancy or will not progress to a chronic disease, but patients must be aware of the triggering factors such as alcohol consumption, dehydration, and fasting. Long-

should be counselled by the healthcare workers during the diagnosis to avoid unnecessary, potentially harmful investigations and prevent accidental adverse drug effects due to the interactions with the physiology of a patient with GS [1].

### PROGNOSIS

range of age-related diseases due to the effective antioxidant/anti-inflammatory properties. The markers of oxidative stress appear condensed in people with Gilbert's syndrome. The overall mortality rate in individuals with mild hyperbilirubinemia due to GS is lower, compared to the general population.19 Patients with mild hyperbilirubinemia secondary to GS have been known to have lower rates of all-cause mortality compared to the general population.

### CONCLUSION

term treatment or medications are not required. But care should be taken with patients having the concurrent disease as the certain drugs such as gemfibrozil-statin combination, or certain chemotherapeutic drugs like may result in harmful effects. Certain pieces of evidence have been observed that give the patients with GS a protective effect. Mortality rates observed for people with Gilbert's syndrome in the general population are approximately half.

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