REVIEW ARTICLE

GILBERT’S SYNDROME- A CONCEALED ADVERSITY FOR PHYSICIANS AND SURGEONS

Ahsan Rasool, Sabir Sabir*, Muhammad Ashfaq**, Umer Farooq**, Muhammad Zatmar Khan, Faisal Yousaf Khan

Ayub Medical College, Abbottabad, Pakistan, *Clinical Fellow Hepatobiliary Anaesthesia, Toronto East General Hospital, Toronto-Canada, **Department of Community Medicine, Ayub Medical College, Abbottabad-Pakistan

Gilbert’s syndrome (often abbreviated as GS) is most common hereditary cause of mild unconjugated (indirect) hyperbilirubinemia. Various studies have been published depicting clinical and pharmacological effects of Gilbert’s syndrome (GS). However GS as a sign of precaution for physician and surgeons has not been clearly established. A systematic study of the available literature was done. Key words of Gilbert’s syndrome, hyperbilirubinemia and clinical and pharmacological aspects of GS were searched using PubMed as search engine. Considering the study done in last 40 years, 375 articles were obtained and their abstracts were studied. The criterion for selecting the articles for thorough study was based on their close relevance with the topic. Thus 40 articles and 2 case reports were thoroughly studied. It was concluded that Gilbert’s syndrome has immense clinical importance because the mild hyperbilirubinemia can be mistaken for a sign of occult, chronic, or progressive liver disease. GS is associated with lack of detoxification of few drugs. It is related with spherocytosis, choliathiasis, haemolytic anaemia, intra-operative toxicity, irinotecan toxicity, schizophrenia and problems in morphine metabolism. It also has profound phenotypic effect as well. The bilirubin level of a GS individual can rise abnormally high in various conditions in a person having Gilbert’s syndrome. This can mislead the physicians and surgeons towards false diagnosis. Therefore proper diagnosis of GS should be ascertained in order to avoid the concealed adversities of this syndrome.

Keywords: Gilbert’s syndrome, hyperbilirubinemia

INTRODUCTION

Gilbert’s syndrome (GS) is hereditary condition causing mild unconjugated hyperbilirubinemia without evidence of liver disease or hemolysis. It was discovered in 1901. The hyperbilirubinemia that occurs in this syndrome is caused by defective UGT1A1 enzyme responsible for glucuronidation by liver. Defect lies in promoter region encoding for the gene. Since this enzyme is involved in drug metabolism, a GS individual is more likely to have drug toxicity. Coexistence of GS with other disease can interfere with their diagnosis as well. The purpose of this review is to elaborate how GS can turn into a concealed adversity for a physician and surgeon.

Search Strategy and Selection Criterion:
PubMed was searched for English language references published during the time period of 1970 to 2012. Combinations of the terms searched included ‘Gilbert’s syndrome’, ‘hyperbilirubinemia’, ‘clinical aspects’, ‘pharmacological aspects’, ‘case report’, ‘coinheritance’. Selection criterion was based on depiction of clinical and pharmacological aspects of gilbert’s syndrome while isolated cases of gilbert’s syndrome were excluded from study.

Epidemiology:
The genetic epidemiology of GS is variable in different ethnic groups around the globe. It is found in up to 6–9% of general population. It is more prevalent in males as compared to females (12.4 in males and 4.8% in females respectively). GS is an autosomal recessive inherited condition; however a clear family history is not always apparent.

Pathophysiology:
GS is caused by reduced activity of enzyme glucuronyltransferase. This causes partial inability of the liver to conjugate bilirubin. UDP-glucuronosyltransferase1 (UGT1A1) gene codes for this enzyme. Defect mostly lies in the promoter region of this enzyme. Its most common cause is homozygous variant of the A (TA) 7TAA promoter polymorphism.

Clinical features:
Spherocytosis, gallstones and GS: Gilbert’s syndrome is closely related with haemolytic anaemia and gallstones. This haemolytic anaemia is caused by spherocytosis of RBCs which if hereditary has coinherence with Gilbert’s syndrome. Gallstones, on the other hand, bears direct coinherence with the Gilbert’s syndrome. In addition to this, the most common complication of a patient of hereditary spherocytosis (HS) is formation of gallstones. These facts make Gilbert’s syndrome a risk factor for gallstone formation.

Schizophrenia and GS: Miyaoaka T. and his co-workers showed a close relationship of this schizophrenia and GS. 20.6% schizophrenic patients

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had mild hyperbilirubinemia.\textsuperscript{11} However this should be considered for further investigation.

\textbf{Conditions elevating serum bilirubin level in GS:} Serum bilirubin concentrations are often less than 3 mg/dl. However, the bilirubin level can rise abnormally high in various conditions in a person having Gilbert’s syndrome.\textsuperscript{12} A number of factors may increase bilirubin in Gilbert's syndrome. Major factors include fasting, infections, dehydration, surgery, physical exertion, and lack of sleep. The subsequent increase in serum concentrations of unconjugated bilirubin can lead to intermittent episodes of (non-pruritic) jaundice.\textsuperscript{13} Symptoms caused by the precipitating factor and not directly by Gilbert’s syndrome, including tiredness occur during episodes of jaundice.\textsuperscript{13} Serum bilirubin level is elevated in menstruation as well.\textsuperscript{14}

\textbf{Harmful effects of hyperbilirubinemia in GS:} The bilirubin level can rise abnormally high in various conditions in a person having Gilbert’s syndrome. This elevation, in turn, has many detrimental effects. This mild hyperbilirubinemia can be mistaken for a sign of occult, chronic, or progressive liver disease.\textsuperscript{15} In neonates, hyperbilirubinemia is the most common clinical condition requiring evaluation and treatment in the new-born and the most common cause for hospital readmission during the first week of postnatal life. The total serum bilirubin (TSB) may rise to hazardous levels that pose a direct threat of brain damage. Acute bilirubin encephalopathy may ensue, frequently evolving into kernicterus, a devastating, chronic and disabling condition characterized by the clinical tetrad of:

a. Choreoathetoid cerebral palsy
b. High-frequency central neural hearing loss
c. Palsy of vertical gaze
d. Dental enamel hypoplasia, the result of bilirubin-induced cell toxicity.\textsuperscript{16}

\textbf{GS can interfere with diagnosis of other diseases:} Unexpected elevation of serum bilirubin level in Gilbert’s syndrome can lead to a situation of dilemma. Parker AE \textit{et al.}\textsuperscript{17} indicated a case report of a 14-year-old girl. She had pain in right-lower quadrant and was jaundiced, describing a two-day history of nausea, non-bilious vomiting, fever to 38.3°C, and peri-umbilical pain. Her abdominal pain subsequently migrated to the right-lower quadrant and she became markedly jaundiced within 24 hours. These signs created a confusing situation. It was difficult to seek out that:

- Should this patient have any further workup for her jaundice before appendectomy?
- Will she require any specific management intra-operatively or postoperatively related to her hyperbilirubinemia?

Finally a diagnosis of Gilbert’s syndrome exacerbated by acute appendicitis on subsequent normal liver-function tests was made. Corresponding adjustment were then ensued. Thus, in a similar way, this syndrome can create puzzling situation for physicians and surgeons.

\textbf{Lack of detoxification of few drugs in GS:} Bilirubin-UGT (UGT1A1 isoform) is one of the several UGT enzyme isoforms responsible for the conjugation of a wide array of substrates, which include carcinogens, drugs, hormones and neurotransmitters.\textsuperscript{18} Thus defective enzymes lead to lack of detoxification of various compounds causing diarrhoea. For example, diarrhoea and neutropenia in patients of colorectal cancer ensues when treated with irinotecan.\textsuperscript{19} Since The UGT1A1 isoform is solely responsible for the metabolism of bilirubin, numerous endogenous hormones, and numerous pharmacologic compounds, including irinotecan, genetic variation in UGT1A (which occurs in GS) correlates with adverse events caused by irinotecan toxicity.\textsuperscript{20} Paracetamol is metabolized by one of the other enzymes also deficient in some people with Gilbert’s syndrome, thus people with this syndrome may have an increased risk of Paracetamol toxicity as well.\textsuperscript{21}

\textbf{GS and intra-operative toxicity:} Special care is required for patients of Gilbert’s syndrome since this can prove havoc on operation table. It is important for the anaesthesiologists to consider the decreased glucuronosyl transferase activity in GS patients while submitting them to anaesthesia in order to prevent intraoperative toxicity.\textsuperscript{22} Since there is low glucuronyl transferase activity in the liver there is a risk for anaesthetic toxicity with a possibility of a catastrophic outcome. Thus it is important for the anaesthesiologists to understand the pathophysiology of the disease and the conditions leading to decreased glucuronyl transferase activity.

\textbf{Morphine metabolism in GS:} Morphine is widely used as analgesic in relieving pain of cancer patients.\textsuperscript{23} It requires glucuronidation for its clearance from blood.\textsuperscript{24} This is catalyzed by UGT2B7, with minor contribution from UGT1A3.\textsuperscript{25} It is immense important to know that in Gilbert's syndrome same family of enzymes is defective. So it can be presumed that Gilbert’s syndrome might be related with defective morphine clearance. This conception was strengthened by a case reporting prolonged sedation, miosis and respiratory depression due to decreased morphine clearance in a patient with Gilbert's syndrome.\textsuperscript{26}

However this conception were abandoned on basis of latest studies, proving that in Gilbert’s syndrome UGT1A1 only is defective and not UGT2B7. Thus posing no detrimental effect on morphine glucuronidation.\textsuperscript{27}
Colorectal cancer and GS: As discussed subsequently, another important aspect of gilbert’s syndrome comes into play while considering colorectal cancer. The common drug prescribed in metastatic colorectal cancer is irinotecan. This is metabolized by same enzyme defective in Gilbert’s syndrome. Lack of metabolism can lead to toxicity which results in severe diarrhoea. All these situations emphasize the need for proper diagnosis of this syndrome in various ailments in order to avoid complications.

Diffuse phenotypic effects: However, Gilbert’s syndrome is considered a phenotypic effect rather than a serious disorder because of its profound beneficial effects. Demographic studies show the people having this syndrome are less likely to have ischemic heart diseases (IHD) and atherosclerosis. These are presumable due to anti-oxidant effect of unconjugated bilirubin. Similarly prevalence of atherosclerosis is inversely related with Gilbert’s syndrome. As compared to normal individuals, lower level of Low Density lipoprotein (LDL), higher level of total antioxidant capacity and high density lipoprotein (HDL) cholesterol are found in Gilbert’s syndrome subjects. Cardiovascular diseases (CVD) other oxidative and inflammatory diseases are less common in individuals having decreased hepatic bilirubin UDP-glucuronosyltransferase activity, decreased bilirubin clearance, and increased serum bilirubin concentrations (as occurs in GS).

Diagnosis:
It is crucial to establish a correct diagnosis and differentiate this syndrome from serious disorders of the liver tissue. Typically, the indirect hyperbilirubinemia is not recognized until after puberty, and it manifests itself during fasting or illnesses. This is because normally hyperbilirubinemia in Gilbert’s syndrome is so mild that there are no obvious symptoms. Diagnostic tests include medical history, physical examination, and blood test. Differential diagnosis by alkaline methanolysis procedure of Blanckaert followed by thin-layer chromatography can discriminate Gilbert's syndrome from healthy subjects, patients with chronic persistent hepatitis and patients with chronic hemolysis. The diagnostic role of the reduced caloric intake test and phenobarbitol treatment in Gilbert's syndrome over normal individuals is also well established.

Management:
Perioperative care in GS: These include minimize fasting and stress by providing adequate glucose infusion the night before surgery and perform the surgery in the morning session and administering analgesia during the intraoperative as well as during the postoperative periods. Avoiding hepatotoxic drugs is paramount factor to be considered as postoperative care.

Analgesics recommended in GS: Chandra A. and his co-workers explained the precautionary measures undertaken in order to avoid uneventful situations while performing a surgery on a patient with GS. Use of Morphine and Paracetamol was despised because of fear of drug toxicity since there is low activity of metabolizing enzymes. Instead epidural anaesthesia appeared a safer option. Nag DS and his co-workers showed that propofol is metabolized by both liver and kidney as compared to thiopentone or ketamine thus providing a greater safety margin. The study also showed that diclofenac sodium and pentazocine used for postoperative analgesia bear a better safety margin.

Treatment:
Gilbert’s syndrome is a mild disorder that typically doesn’t need medical treatment. People with the disorder lead normal, healthy lives. However in case of hyperbilirubinemia, medicines that lower bilirubin levels are administered. Since phenobarbital enhances glucuronide formation, its administration significantly reduces the level of unconjugated serum bilirubin in patients with acute hepatitis or Gilbert's syndrome.

Need for review:
Various studies have been published depicting clinical and pharmacological effects of GS. However GS as a sign of precaution for physician and surgeons has not been clearly established. Gilbert’s syndrome is associated with many confusing sign and symptoms. Its occurrence can easily lead to false positive results in various diseases, making a patient prone to false diagnosis and hence wrong treatment. Since it is most common hereditary cause of unconjugated hyperbilirubinemia, occurring in 3% to 10% of general population, it requires special attention. As the liver has defective battery of UGT enzymes, detoxification of various drugs cannot ensue and leading to drug intoxications. Because of this intoxication in undiagnosed GS can become a serious emergency for physician. This drug intoxication effect must also be kept in consideration by surgeons in order to avoid anaesthesia intoxication. Undiagnosed GS can also lead to confusing signs and symptoms creating a dilemma for both physicians and surgeons.

RECOMMENDATION
In order to avoid the fore-mentioned hazardous results and dilemma, a thorough understanding and proper diagnosis of GS should be ascertained before every clinical (medical as well as surgical) venture.
REFERENCES


Address for Correspondence:
Ahsan Rasool, Ayub Medical College, Abbottabad-Pakistan
Cell: +92 332 999 9630
Email: ahsanrasool.dr@gmail.com