

Asymptomatic Unconjugated Hyperbilirubinemia (Gilbert Syndrome) Among Saudis in Jeddah

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Gilbert syndrome is probably one of the most common syndromes known; it is defined as hereditary, chronic, nonhemolytic, mildly unconjugated hyperbilirubinemia associated with impaired hepatic clearance of bilirubin but with otherwise normal hepatic structure and function. The syndrome is almost certainly part of the spectrum which includes Crigler-Najjar syndrome. Its prevalence among Caucasians has been documented to be 3% to 7%. However, its prevalence in Arabs (specifically Saudis in our report) has not been studied before. This study aims to find the prevalence of the syndrome among Saudis. This would be helpful in determining the probability of Gilbert syndrome in the workup of a Saudi patient with unexplained unconjugated hyperbilirubinemia occasionally discovered on routine liver function test analysis.

Material and Methods

Blood samples were obtained from 450 randomly selected Saudi national volunteers from university students, hospital and university staff. They were asked to fast for a period of at least 12 hours and 3 mL of blood were then withdrawn from each and transported in a dark box to avoid exposure to light. The samples were centrifuged at 300 rpm for 15 minutes; plasma was separated from red blood cells and kept frozen until investigation was carried out. All samples with total bilirubin level equal to or more than 20 mmol/L were further investigated for direct bilirubin using the automated analysis of B.M. Hitachi 705 which uses the method of DPD (2,5, dichlorophenyl diazonium). Quality control samples of Ciba Corning normal control, Lot No. 036801 and abnormal control, Lot No. 025802 were run intermittently. Volunteers with a total bilirubin level of 20 mmol/L or more mainly consisting of unconjugated type were used for the second stage investigation which included a nonfasting blood sample. If a normal bilirubin level was detected, the patient was asked

to fast again and a second bilirubin level was measured. If the fasting bilirubin was repeatedly elevated, the volunteer was then included in the third stage of the investigation. This consisted of complete blood count, sickling test, G6PD level, blood film examination, liver function test, hepatitis screening, liver and gallbladder ultrasonography and serum electrophoresis for hemoglobinopathies. These tests were meant to exclude gallstones and functional or structural liver diseases. Drug history was also fully obtained to exclude the chance that a patient has a high bilirubin level due to drug side effects. If all tests were negative and the volunteer had a normal physical examination, he/she was diagnosed as having Gilbert syndrome.

Results

A total of 450 samples from 450 volunteers were examined. There were 274 females (60.9%) and 176 males (39.1%). The age range was from 20 to 60 and the mean age was 36.3 ± 13.3 . There were 16 cases positively identified to have asymptomatic unconjugated hyperbilirubinemia (Gilbert syndrome). Details of these patients are shown in Table 1. Fifty percent of Gilbert syndrome

TABLE 1. Details of individuals diagnosed with Gilbert syndrome.

No.	Age / Sex	Fasting - Total bilirubin blood level mmol/L	Conjugated bilirubin blood level mmol/L
1	20 / male	46	4.5
2	23 / male	32	0.0
3	23 / female	22	0.0
4	24 / male	47	4.0
5	25 / male	40	1.0
6	25 / female	31	0.0
7	29 / female	40	3.0
8	29 / male	27	4.0
9	32 / female	27	4.0
10	33 / female	20	1.0
11	37 / male	20	0.0
12	41 / male	29	1.0
13	44 / female	22	2.0
14	45 / male	31	3.0
15	50 / male	23	2.0
16	60 / male	23	2.0

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patients were below the age of 30 years, 10 of the 16 patients were males, the remaining were females, five (patients 1, 2, 4, 5, 7) recalled becoming jaundiced during Ramadan, during the winter season or after stress. Only three patients were having nonspecific symptoms such as abdominal discomfort, fatigue and malaise.

Discussion

Gilbert syndrome is defined as hereditary, chronic, nonhemolytic, mildly unconjugated hyperbilirubinemia associated with the impaired hepatic clearance of bilirubin but otherwise normal hepatic structure and function.¹ In this study, the diagnosis of Gilbert disease was based on the presence of chronic, fluctuating, unconjugated hyperbilirubinemia which increased with fasting, associated with normal liver function tests, complete blood count, hepatitis serology, red cell osmotic fragility, electrophoretic pattern of hemoglobin, G6PD level and ultrasound of the liver along with absent signs of hemolysis and noncontributory drug history. The absence of the above criteria in the setting of unconjugated hyperbilirubin was also considered by others as diagnostic of Gilbert syndrome.¹⁻³ The familial nature of Gilbert syndrome was initially reported by the French physician who first described the disease, Augustin Nicolas Gilbert.⁴ Because positive family history was reported in less than 4% of patients, 27% to 55% of siblings and 16% to 26% of parents,^{5,6} the familial history cannot be considered an essential part of the diagnostic workup of Gilbert disease. The accumulated data, however, indicate that Gilbert syndrome is inherited as an autosomal dominant trait and that patients are heterozygous for a single abnormal gene.¹ Plasma bilirubin level in normal subjects varies with gender; the postpubertal males have higher levels than females⁷ and this may be due to the effect of female hormones on UDP-glucuronosyltransferase.⁸ However, the condition is more frequent in males, even allowing for this natural difference, as the reported male to female ratio is 2.7:1.⁹ In this study the male:female ratio is 2.7:1. This is almost the same as reported in non-Saudi populations. Genetic studies indicate that Gilbert syndrome is inherited as an autosomal dominant trait and the sex difference in prevalence suggests the possibility of incomplete penetration of the affected gene in both males and females. The reported prevalence of Gilbert syndrome varies from 3% to 12% in various ethnic groups^{5,8-10} but has not been previously examined in Saudis. In this study of a Saudi population, the prevalence was 3.6% (16 out of 450). This is comparable to previous reports from other populations.

It is rare for Gilbert syndrome to be recognized before puberty and the diagnosis is discovered most often following intercurrent illness, fasting for surgery or during

the month of Ramadan or after any stress (one of the patients is a medical student who turns yellowish just before anatomy exam!) and it usually occurs in the second or third decade of life. The mean age of patients with Gilbert disease is 33.8 ± 11.5 years, which is also comparable to other previous reports. Apart from fluctuating jaundice which increases by previously mentioned factors, some patients complained of a variety of nonspecific symptoms such as malaise, fatigue and abdominal discomfort. Three patients in this series had such symptoms. Intravenous nicotinic acid or oral phenobarbital may cause elevation or depression (respectively) of the bilirubin level; this phenomenon can be used in the diagnosis of Gilbert syndrome when there is uncertainty regarding the diagnosis.^{2,3} Because of the benign nature of the disease, none of the patients in this study were started on any medication and they were only offered assurance and explanation of the disease.

In conclusion, the prevalence and characteristics of Gilbert syndrome in the Saudi population is comparable to its prevalence in non-Saudi populations elsewhere in the world.

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