

THE PREVALENCE OF ISOLATED UNCONJUGATED HYPERBILIRUBINAEMIA (GILBERT'S SYNDROME) IN SUBJECTS ATTENDING A HEALTH SCREENING PROGRAMME IN SINGAPORE

K A Gwee, E S C Koay, J Y Kang

ABSTRACT

We retrospectively studied the prevalence of hyperbilirubinaemia in 1,296 consecutive subjects attending a hospital health screening programme over an eighteen-month period. Sixty-four subjects (5%) had elevated bilirubin levels. Forty-one subjects (3.2%) had isolated unconjugated hyperbilirubinaemia. These subjects probably had Gilbert's syndrome. Recognition of this common benign condition is important to avoid unnecessary investigations.

Keywords: unconjugated hyperbilirubinaemia, Gilbert's syndrome, prevalence, health screening, liver function tests.

SINGAPORE MED J 1992; Vol 33: 588-589

INTRODUCTION

A chance finding of mild hyperbilirubinaemia on routine biochemical screening is not uncommon^(1,2). With routine health screening gaining popularity in Singapore, physicians will increasingly encounter subjects with elevated bilirubin levels. Some of these subjects have Gilbert's syndrome – a benign condition in which serum levels of unconjugated bilirubin are elevated in the absence of structural liver disease and overt haemolysis. In order to determine the prevalence of this phenomenon in Singapore, we studied subjects attending a health screening programme.

MATERIALS & METHODS

One thousand two hundred and ninety-six subjects attended the National University Hospital's multiphasic health screening programme between May 1989 and December 1990. Each subject had a detailed history taken and underwent a full physical examination. Haematological and biochemical analyses were performed on a fasting sample of blood. Bilirubin concentrations, both total and differential, were measured on the Kodak Ektachem 700 XR autoanalyser (using dry chemistry and slide technology) (Serum bilirubin concentration reference range: 0 - 22 $\mu\text{mol/L}$). Other tests of liver function performed included

serum transaminases and alkaline phosphatase. Hepatitis B serology (HBsAg & anti-HBs) was also done for all subjects and where indicated, haemoglobin electrophoresis.

Where indicated, subjects with abnormal liver function test results were further investigated with ultrasound study of the liver. Serum vitamin B₁₂ levels were measured in subjects with macrocytic anaemia.

The charts of all subjects with unconjugated hyperbilirubinaemia were reviewed. We looked for significant alcohol consumption, clinical evidence of liver disease and blood indices suggesting haemolysis or ineffective erythropoiesis. Follow-up attendances were also reviewed to determine if any liver or haematological disease subsequently developed.

Categorical data were analysed by the X² test, while numerical data were analysed by the Student's t test: probability values below 0.05 were considered significant.

RESULTS

A. Patient Characteristics

Our study population consisted of 754 male and 542 female subjects (1.4 male to 1 female). Their ages ranged from 16 to 87 with a mean of 45.7 years. The majority, 1,171(90%) were Chinese; there were 35(3%) Indians, 11(1%) Malays and 79(6%) subjects of other races.

B. Hyperbilirubinaemia with Associated Abnormalities

Sixty-four subjects (5%) had elevated bilirubin levels. Of these, 23 had other associated abnormalities. In four subjects with associated mild anaemia and microcytosis, haemoglobin electrophoresis confirmed a diagnosis of thalassaemia. In this haemoglobinopathy both ineffective erythropoiesis and peripheral haemolysis contribute to the hyperbilirubinaemia. In two subjects with macrocytosis, a diagnosis of pernicious anaemia, a condition associated with ineffective erythropoiesis, was made. In 3 subjects ultrasound examination of the hepatobiliary system revealed gallstone disease which could have accounted for the jaundice. Fourteen other subjects had other associated liver function test abnormalities: 3 had significant alcohol consumption, 5 had unexplained mildly elevated serum transaminase levels and 6 had isolated raised serum alkaline phosphatase levels.

C. Isolated Unconjugated Hyperbilirubinaemia

Forty-one subjects were found to have unconjugated hyperbilirubinaemia with otherwise normal liver function tests and no evidence of haemolysis or other diseases to account for their elevated bilirubin levels. None of these subjects were

Department of Pharmacology
National University of Singapore
10 Kent Ridge Crescent
Singapore 0511

K A Gwee, MBBS, MMed (Int Med), MRCP (UK)
Lecturer

Department of Pathology
National University of Singapore

E S C Koay, PhD, FAACB
Senior Lecturer

Division of Gastroenterology
Department of Medicine
National University Hospital
Lower Kent Ridge Road
Singapore 0511

J Y Kang, MD, FRCP, FRCPED, FRACP
Associate Professor and Head

Correspondence to: A/Prof J Y Kang

positive for HBsAg. A review of the case records of all the above 41 subjects, 1 to 2 years after their initial visit, also showed that none of them had developed any significant liver or haematological disease. These subjects have Gilbert's syndrome.

The prevalence of isolated unconjugated hyperbilirubinaemia in our health screening population is therefore 3.2%. Unfortunately reticulocyte counts were not done as part of the haematological screening, but an analysis of the haemoglobin levels of our patients suggested that they were all within the normal range (mean Hb for males 15.6g/dL, for females 13.9g/dL).

Although there were more male subjects with isolated unconjugated hyperbilirubinaemia, the sex difference was not statistically significant (see table I). The mean bilirubin level was significantly higher in male subjects than in female subjects (see table I).

Table I – Mean bilirubin concentrations of subjects with Gilbert's Syndrome

	Combined	Male	Female
Total No. of subjects	1296	754	542
No. with Gilbert's Syndrome	41	28	13
%	3.2	3.7 *	2.4
Bilirubin level Mean	27.4	28.7**	24.7
Standard Error		1.15	0.75

* p = 0.24 ** p < 0.05

The mean age of our Gilbert's syndrome subjects was 43.9 years (SD: 13.3). This was not significantly different from that of subjects with normal bilirubin and normal liver enzymes which was 45.7 years (SD: 12.2).

DISCUSSION

The present study demonstrates that isolated unconjugated hyperbilirubinaemia is common in an apparently healthy population attending health screening. As our study population was not selected in terms of liver or other diseases, we feel that the prevalence of Gilbert's syndrome in our series should approximate that in the general population, with two reservations. Firstly, the racial distribution of our study population is not representative of the general population. Secondly, in view of the intermittent nature of the hyperbilirubinaemia in Gilbert's syndrome, the possibility of underestimation cannot be discounted. Population studies by other investigators^(1,2) are also based on single sample analyses and reported prevalence rates ranging from 2% to 6% comparable to those in the present study.

Although we failed to show a convincing sex difference, males predominate in ratios of approximately 4:1 in most series⁽³⁾. The sex difference is believed to be due to the higher bilirubin concentrations in normal males than in females. The higher mean bilirubin concentration in our male subjects as compared with the female subjects is consistent with population studies which show that in general men have higher plasma bilirubin concentrations than women⁽⁴⁾. A study of bilirubin kinetics⁽⁵⁾ found a lower hepatic bilirubin clearance per kg body weight in males compared to females. Perhaps the reference range for bilirubin should be adjusted for sex.

Gilbert's syndrome was first described by two Frenchmen, Gilbert and Lereboullet. The familial nature has been recognised since that first report. Powell⁽⁶⁾ studied the families of 42 subjects and suggested that inheritance is autosomal dominant with incomplete penetrance. However, the heterogeneity of this disorder has complicated many family studies so that the mode of inheritance has not been clearly defined.

The nature of this 'disease' is not entirely clear. Gilbert's syndrome may be a distinct disease entity or may merely rep-

resent an extreme expression of normality. Population studies⁽⁴⁾ which show a bimodal distribution of bilirubin concentrations support the existence of a well-defined entity separable from 'normal' subjects. However, in the two largest population studies^(1,7), bilirubin levels fitted a straight line on a log-probability curve, disputing the existence of subjects with isolated unconjugated hyperbilirubinaemia as a separate population.

No single enzyme defect readily explains all of the observed abnormalities. The only consistent defect found in previous studies is a mild deficiency of the hepatic conjugating enzyme, uridine diphosphate glucuronyl transferase⁽⁸⁾. Other abnormalities that have been reported in subjects with Gilbert's syndrome include a mild and fully compensated state of haemolysis as well as increased hepatic haem turnover⁽⁸⁾. In addition hepatic transport anomalies like mildly abnormal bromsulphalein clearance and indocyanine green uptake have been noted in association with Gilbert's syndrome. Considering the multiplicity of associated defects, it appears likely that Gilbert's syndrome represents a heterogeneous group of pathogenetic defects.

Gilbert's syndrome is not associated with any specific symptoms⁽⁷⁾. However, an individual with previously unrecognised Gilbert's syndrome, who develops an intercurrent illness eg a febrile illness, may develop more pronounced hyperbilirubinaemia as a result of caloric withdrawal. Hence symptoms of the intercurrent illness eg fever, anorexia, nausea and vomiting, may be wrongly attributed to Gilbert's syndrome. Indeed, a reduced caloric intake test⁽²⁾, where a two to three fold increase in plasma unconjugated bilirubin concentration is observed within 48 hours of reducing the daily intake to 400 calories has been recommended to confirm the diagnosis of Gilbert's syndrome. However, subsequent work has shown that this test is neither sensitive nor specific⁽⁷⁾.

Recognition of this condition is important to distinguish it from more serious causes of liver function test abnormalities and to avoid unnecessary investigations. If a subject has unconjugated hyperbilirubinaemia with otherwise normal liver function tests, and normal blood and reticulocyte counts exclude haemolysis, a presumptive diagnosis of Gilbert's syndrome can be made. The subject should then be followed up for the next 12 to 18 months with two to three visits, during which if no further laboratory abnormalities develop, a definitive diagnosis can be made. The subject can then be reassured of the excellent prognosis and normal life expectancy, and physicians can confidently support insurance and employment applications⁽³⁾.

ACKNOWLEDGEMENTS

The authors would like to thank Professor Tan Yew Oo and all the physicians in the Department of Medicine for allowing us to study their patients and Associate Professor Aw Tar Choon, Chief of Department of Clinical Chemistry, National University Hospital, for help and advice.

REFERENCES

- Bailey A, Robinson D. Does Gilbert's disease exist? *Lancet* 1977; 1: 931-3.
- Owens D, Sherlock S. Diagnosis of Gilbert's syndrome: role of reduced caloric intake test. *Br Med J* 1973; iii: 559.
- Billing BH. Abnormalities in bilirubin metabolism associated with jaundice. In: Schiff L, Schiff ER, eds. *Diseases of the Liver*. 6th ed. Philadelphia: JB Lippincott, 1987: 103-27.
- Owens D, Evans J. Population studies on Gilbert's syndrome. *J Med Genet* 1975; 12: 152-6.
- Berk PD, Howe RB, Bloomer JR, Berlin NJ. Studies of bilirubin kinetics in normal adults. *J Clin Invest* 1969; 48: 2176-90.
- Powell LW, Hemingway E, Billing BH, Sherlock S. Idiopathic unconjugated hyperbilirubinemia (Gilbert's syndrome). A study of 42 families. *N Engl J Med* 1967; 277: 1108-12.
- Olsson R, Stigendal L. Clinical experience with isolated hyperbilirubinaemia. *Scand J Gastroenterol* 1989; 24: 617-22.
- Gollan J, Schmid R. Bilirubin metabolism and hyperbilirubinaemic disorders. In: Wright R, Millward-Sadler GH, Alberti KGMM, Karan S, eds. *Liver and Biliary Disease*. 2nd ed. Philadelphia: WB Saunders, 1985: 301-57.