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Gilbert's syndrome in patients with gallbladder stones

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Summary

Patients with Gilbert's syndrome suffer from an abnormality which makes them jaundiced from time to time. A number also develop gallstones and come to cholecystectomy. If this condition has not been recognized these patients may subsequently run the risk of unnecessary operations on their bile ducts from the mistaken assumption that the intermittent episodes of jaundice which are a feature of the syndrome are due to a stone which has been left behind. Such a case history is reported here.

In an attempt to determine how frequently these conditions coexist a prospective study was carried out on patients about to undergo cholecystectomy for stones in the gallbladder. Gilbert's disease was found to be present in 2 of 67 males (3.2% ± 0.8%) but not in 184 females. Hence it seems that about 1 in every 30 males subjected to cholecystectomy may be expected to have this abnormality.

It is suggested that this places an obligation on the clinician to have liver function tests done on at least two occasions preoperatively in male patients with cholelithiasis in an attempt to detect this abnormality and avoid this surgical pitfall.

Introduction

Unconjugated hyperbilirubinaemia in the absence of overt haemolysis may be associated with heart disease, haematological, gastrointestinal, and hepatobiliary disorders, and various infections[1]. It can also be congenital, the commonest variety being Gilbert's syndrome[2].

In 1900 Gilbert *et al.* published an account of a heterogeneous group of patients characterized by the intermittent presence of elevated levels of unconjugated bilirubin in their blood[3]. Later these authors classified such patients into three categories: *'cholémie physiologique'*, *'cholémie simple familiale'*, and *'ictère chronique simple'*[4]. Gilbert's syndrome refers to those patients falling into the second category, while patients in the last category should be regarded as cases of haemolytic anaemia[5,6].

The criteria on which the diagnosis of Gilbert's syndrome is based have been summarized by Powell *et al.*[7]:

1) Elevated levels of unconjugated bilirubin in plasma on three occasions.

2) No past history of viral hepatitis.

3) No abnormal physical findings apart from icterus.

4) All routine tests of liver function normal.

5) Haematological investigations, including haemoglobin, peripheral film, reticulocyte count, and erythrocyte fragility, show no evidence of haemolysis.

6) Liver biopsy normal.

Studies of affected families have suggested that Gilbert's syndrome is probably inherited as an autosomal dominant, patients being heterozygous for a single mutant gene[8].

From time to time in this condition there is a mild elevation of the plasma unconjugated bilirubin concentration (1–4 mg/100 ml)[9]. Powell *et al.*[7] reported the range of total plasma bilirubin to be 0.1–6.2 mg/100 ml in 20 patients, of whom 17 had a maximum level of less than 4.0 mg/100 ml. In a more recent study the mean level of total plasma bilirubin was 1.8 ± 0.2 mg/100 ml[10].

Although overt haemolysis precludes the diagnosis of Gilbert's syndrome, studies on the survival of red blood cells revealed that in 42% of such patients the erythrocyte life span was reduced when 27 days was taken to be the lower limit of normal for the half-life ($T\frac{1}{2}$) of ^{51}Cr-labelled red cells[7]. Berk *et al.*[11] studied the clearance of injected radioactive bilirubin from the blood in 11 patients with Gilbert's syndrome and concluded that these patients had a defect in the uptake and conjugation of bilirubin. Arias and London[12] had already shown that 2 patients with Gilbert's syndrome had a deficiency of uridine diphosphate glucuronic acid transferase activity in the liver and suggested that this might be the cause.

The retention of bromsulphalein (BSP) in plasma has been studied in such patients with conflicting results. Normal BSP clearance has been reported by Dameshek and Singer[6] and Powell *et al.*[7] Berk *et al.*[13], however, found that 9 out of 26 patients retained more than 5% of the injected dose of BSP in their plasma at 45 minutes.

The coexistence of gallstones with Gilbert's syndrome has been reported: gallstones were detected on cholecystography in 4 of 53 patients by Foulk *et al.*[14] and had necessitated cholecystectomy in 2 of 55 patients studied by Powell *et al.*[8] The incidence of Gilbert's syndrome in an unselected group of patients with cholelithiasis has not previously been recorded, however, and we report here our findings on this. It should be noted that we have excluded patients known to have common bile duct stones because once the biliary tract has become involved in calculous disease the diagnosis of Gilbert's syndrome becomes difficult. The presence of calculi in the bile duct is likely to produce abnormalities in liver function which may mask the typical picture of this syndrome in that frequently the plasma bilirubin and alkaline phosphatase levels will be found to be elevated.

Case materials and methods

All patients admitted to the Professorial Surgical Unit at The London Hospital for elective cholecystectomy for gallbladder stones during the 8-year period 1965–72 were included. There was a total of 247 patients, of whom 63 were men.

An attempt was made to exclude the diagnosis of Gilbert's syndrome in these patients. Liver function tests were performed at the initial outpatient visit and at least once again after admission. The combination of mild hyperbilirubinaemia (<4 mg/100 ml) with no appreciable increase in the conjugated fraction and a normal alkaline phosphatase value was regarded as an indication for further preoperative investigation. A reticulocyte count and red cell osmotic fragility test were carried out to exclude a haemolytic cause for the hyperbilirubinaemia. Erythrocyte survival was assessed with ^{51}Cr and the percentage retention of BSP in plasma estimated 45 minutes after intravenous injection (5 mg/kg

body weight). Intravenous cholangiography was undertaken when the biliary tree was not satisfactorily delineated by oral cholecystography, and liver biopsy and peroperative cholangiography were performed at operation when the diagnosis was suspected.

Findings

Two patients, both males, were found to have Gilbert's syndrome, giving a male incidence of 3.2 ± 0.8% with 95% confidence limits.

Case 1 A 38-year-old man presented in December 1965 with a sudden onset of right-sided abdominal pain. On physical examination he was slightly jaundiced and was tender in the right hypochondrium. At that time the plasma bilirubin level was 2.5 mg/100 ml (unconjugated fraction 2.0 mg/100 ml). The reticulocyte count was 2% with a $T\frac{1}{2}$ for ^{51}Cr-labelled red cells of 26 days. Oral cholecystography demonstrated gallbladder stones. The results of the investigations are summarized in the table.

The acute attack subsided and he was discharged to be observed over a period of about a year, during which he suffered recurrent attacks of pain and we referred him for a second opinion to the Royal Free Hospital, London, where the diagnosis of Gilbert's syndrome and gallstones was confirmed. The gallbladder was excised in March 1967 and contained three 'mulberry' stones. The liver appeared normal and was biopsied. Peroperative cholangiography confirmed that the biliary tree was normal. Histological examination showed no evidence of gallbladder inflammation and the liver architecture was normal, although an accumulation of a yellow-brown pigment was noted in some cells with a tendency towards a centrilobular distribution.

Since cholecystectomy the patient has been asymptomatic.

Routine liver function tests were normal in the patient's father, mother, and only child.

Case 2 A 42-year-old man presented in October 1968 with a 4-year history of recurrent epi-

Details of two patients with Gilbert's syndrome

	Case 1	*Case 2*
Age (years)	38	42
Follow-up (years)	6	5
Plasma bilirubin		
No of estimations	13	9
No of normal estimations (<1.0 mg/100 ml)	6	4
Range (mg/100 ml)	0.5–3.2	0.8–1.9
Plasma alkaline phosphatase		
No of estimations	11	9
Range (KA units)	5.0–11.3	7.6–12.4
Plasma retention of BSP (%)	<1, 2	7
Reticulocyte count (%)	2	<2
^{51}Cr $T\frac{1}{2}$ (days)	26	29
Oral cholecystogram	Stones in a functioning gallbladder	Stones in a functioning gallbladder
Intravenous cholangiogram	Normal bile ducts	Normal bile ducts
Peroperative cholangiogram	Normal bile ducts	Normal bile ducts
No of stones removed from gallbladder	3	7
Composition of stones	Cholesterol, calcium, bilirubin	Calcium, bilirubin
Histology		
Gallbladder	No inflammation	Chronic inflammation
Liver	Normal architecture Lipochrome present (centrilobular)	Normal architecture

gastric pain. He claimed that he had never been jaundiced and that the colour of his urine and stools had not altered during attacks of pain. There was no history of hepatobiliary disorder in his blood relatives. He had never received a blood transfusion, was taking no drugs, and had not knowingly been in contact with a case of infectious hepatitis.

On physical examination the sclerae were faintly icteric and there was tenderness in the right hypochondrium. Neither the liver nor the spleen was palpable.

The results of investigations are summarized in the table. Apart from an intermittently raised unconjugated fraction of the plasma bilirubin all routine liver function tests and haematological studies were normal. BSP retention in plasma was 7% 45 minutes after intravenous injection. Oral cholecystography and intravenous cholangiography showed stones confined to the gallbladder.

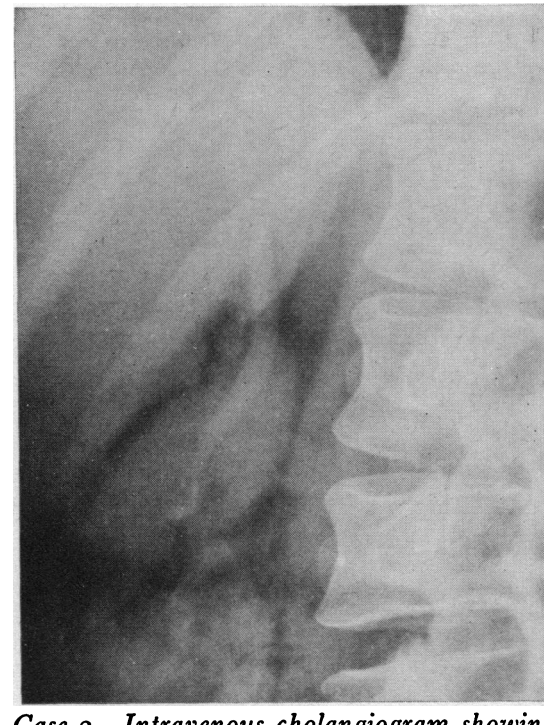
At operation the gallbladder was thickened but all other viscera, including the extrahepatic ducts, liver, and spleen, appeared normal, the normality of the biliary tree being confirmed by operative cholangiography. The 7 stones present were principally composed of calcium and bilirubin. Histologically the gallbladder showed chronic inflammation and the liver was entirely normal. Postoperative recovery was uneventful.

He has attended for follow-up at irregular intervals and states that the epigastric pain is less severe but other symptoms, including flatulence, nausea, and lassitude, have not been affected. He has also sought advice from two other hospitals. In one he was told that X-rays had revealed an abnormally wide bile duct. He was advised that exploration of the ducts would be necessary but declined and after a lapse of some months reattended our follow-up clinic. At this time (June 1973) routine liver function tests were normal apart from mild hyperbilirubinaemia (1.8 mg/100 ml), retention of BSP in the plasma remained raised (8%), and intravenous cholangiography showed a normal biliary tree (see figure).

Discussion

There is evidence that about 5% of patients with Gilbert's syndrome have gallstones[8,14]. Previous experience had indicated to us that such patients may have repeated and unnecessary operations on their common bile ducts. Since 1965 therefore we have screened patients preoperatively in the way described above to try to avoid this surgical pitfall and also to estimate the incidence of Gilbert's syndrome in an unselected group of patients with gallbladder stones.

In Gilbert's syndrome the level of the plasma bilirubin is sometimes raised and this may be further increased by emotion, exercise, or alcohol consumption, but the response is variable[14,15]. Sometimes, however, it will be found to be normal, and indeed if the patient is taking drugs such as barbiturates the level may be depressed and remain consistently normal[16]. It is essential therefore that liver function tests should be carried out on more than one occasion and that these should be done preoperatively. Recently tests have been devised in an attempt to refine the diagnosis. Owens and Sherlock[10] found that after a reduced caloric intake (400 kcal/day) a significantly greater rise



Case 2 Intravenous cholangiogram showing normal bile ducts (1973).

in the plasma unconjugated bilirubin occurred in patients with Gilbert's syndrome than in normal subjects, but only when the initial concentration of bilirubin was raised. Fromke and Miller[15] reported a characteristic prolongation of hyperbilirubinaemia in response to intravenous injection of nicotinic acid in 12 such patients and recently Davidson *et al.*[17] concluded that this test was more reliable and less time-consuming than the reduced caloric intake test.

The criteria for the diagnosis of this condition mentioned above seemed to be fulfilled in the 2 cases reported, although it could be argued that the preoperative jaundice in Case 2 might have been related to cholecystitis[1]. This is considered unlikely since there was no histological evidence of acute inflammation in the gallbladder. Furthermore, intermittent unconjugated hyperbilirubinaemia has persisted in both patients during the period of follow-up, 6 and 5 years respectively.

If it is established that the patient suffers from intermittent attacks of jaundice due to an abnormality such as this before he is subjected to surgery for his gallstones it will be known that the jaundice will recur after the operation. The surgeon will then (as occurred in Case 2) want good evidence from elevations of plasma alkaline phosphatase and from the demonstration of radiological abnormalities in the duct system before he resorts to exploration. His task will be further simplified if peroperative cholangiography at the time of cholecystectomy had demonstrated that the ducts were normal.

Where the diagnosis of Gilbert's syndrome has not been excluded before the first operation, however, it seems to us equally important to try to exclude it in those patients who develop mild fluctuating jaundice after cholecystectomy, particularly if peroperative cholangiography had revealed normal ducts. Here again a normal plasma alkaline phosphatase and intravenous cholangiogram should suggest this possibility.

The incidence of this syndrome in the normal population is in doubt. Kornberg[18] reported 8 cases of non-haemolytic unconjugated hyperbilirubinaemia as a result of random observations on a group of less than 100 medical students. The exact number of individuals in his study and the number of biochemical estimations on each are not recorded, although the author remarked that there was a consistent elevation in the unconjugated fraction over many months. Some of these students, however, appear to have been exposed to infection and hepatotoxic substances and their inclusion as examples of Gilbert's syndrome may be suspect. Nevertheless, in a further study of 120 first- and second-year students 10 possible cases were detected[18].

The incidence of the condition in men as distinct from women has been reported as 49 out of 53 cases (92.4%)[14] and 17 out of 20 cases (85%)[7]. It is therefore predominantly a disease of males. From our data it would appear that less than 1% of patients with gallbladder stones have Gilbert's syndrome, but when males alone are considered the observed incidence was $3.2 \pm 0.8\%$ with 95% confidence limits. This is not inconsistent with the incidence of this condition in healthy people as reported by Kornberg[18]. We have been unable to find any further studies of this nature in the literature. Liver function tests in most of our patients were carried out on only 2 occasions, usually 2–3 months apart. A greater number of tests over a longer period might be expected to have revealed a higher incidence. The number of patients we studied is small and more data are required before final conclusions can be drawn. Until these are available, however, it would appear that about 1 in every 30 men

with cholelithiasis may also have Gilbert's syndrome.

In our view, therefore, this places an obligation on the clinician to carry out liver function tests on at least two occasions on male patients before cholecystectomy. Similarly, when the diagnosis of Gilbert's disease has been made it is equally important to emphasize to the patient that if in the future he should seek advice elsewhere this information should be passed on to the clinician.

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