

GILBERT'S DISEASE

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and

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Gilbert's disease is characterized by intermittent jaundice with hyperbilirubinemia giving an indirect Van den Bergh reaction in the absence of clinical and laboratory evidence of hepatocellular disease or increased hemolysis. Though first described in 1901 as Simple Familial Cholemia (Gilbert and Lereboullet, 1901) it was not till 1920 that Meulengracht emphasised the characteristic features of the syndrome and later (1939) proposed the term icterus intermittens juvenilis. The first major contribution in the English literature on this condition was by Rozendaal, Comfort and Snell (1935) and later Comfort (1945) discussed the syndrome under the title Constitutional Hepatic Dysfunction. Dameshek and Singer (1941) discussing its occurrence in families called it familial non-hemolytic jaundice. But it was only after 1950 that it was increasingly mentioned in medical textbooks: Principles of Internal Medicine (Harrison, 1950), Textbook of Medicine (Cecil and Loeb, 1955), Price's Textbook of the Practice of Medicine (Hunter, 1956), and Pathology for the Physician (Boyd, 1958). In this paper the clinical and laboratory findings of a patient with Gilbert's disease are described: the aim being to draw attention to this benign condition with an excellent prognosis.

CASE REPORT

S.T.A., an Indian male hospital attendant aged 40, was admitted to hospital in 1956 and 1958 and followed up as an out-patient for a multiplicity of vague complaints, the most frequent being pain in the abdomen and a sense of fullness in the epigastrium. The only constant feature noticed was his jaundice. No other abnormal physical signs were detected. The jaundice was first noticed at the age of fifteen and according to his brother, fluctuated in intensity. There were periods of two to three months when the jaundice was more intense and other periods when it was less noticeable. No history of an acute episode of jaundice, malaise,

fever, loss of appetite or weakness was obtained. There was no history of alcoholism.

His father, mother and two sisters were said to be anicteric and healthy but could not be examined as they were in India. His brother aged 35 was examined by one of us (T.C.T.) and found to be healthy with a normal serum bilirubin level.

On 20th January 1958, he was admitted to hospital following an acute attack of epigastric pain. Clinically no abnormality was detected. Barium meal and barium enema examinations and a cholecystogram were reported as normal. Serum bilirubin was 6 mg.%, but other liver function tests were normal and the urine was free of bile with only a trace of urobilinogen. A liver biopsy revealed normal liver tissue (Dr. K. K. Tan).

He was lost to follow up thereafter till 3rd May 1966 when he was admitted to hospital complaining of vague left-sided chest pain for 3 days.

On examination he was afebrile and jaundiced. Clinically no abnormality was detected in the cardiovascular system. The liver and spleen were not palpable and the electrocardiogram was normal.

INVESTIGATIONS

a) Tests to exclude hepatocellular or biliary disease

	9.5.66	6.6.66
Total serum bilirubin	5.0 mg. %	4.2 mg. %
Conjugated bilirubin	0.2 mg. %	0.5 mg. %
Unconjugated bilirubin	4.8 mg. %	3.7 mg. %

Urine: No bile; urobilinogen trace only in repeated specimens; coproporphyrin and porphobilinogen were not detected. E.S.R. 2 mm./hour. Serum proteins 7.3 Gm.%; albumin 4.0

Gm.%, globulin 3.3 Gm.%. Serum alkaline phosphatase 9.0 K.A. units; serum isocitric acid dehydrogenase 360 units (normal range 60-360 units); serum glutamic-pyruvic transaminase 125 K.U. (normal range 30-110 K.U.); serum glutamic-oxaloacetic transaminase 103 K.U. (normal range 35-125 K.U.). The prolonged bromsulphthalein test showed 2% dye retention at 45 minutes. No dye was detected at 90, 150 and 210 minutes. A cholecystogram revealed normal concentration by the gall bladder with no evidence of gall stones. Liver biopsy again showed normal liver tissue (Dr. K.K. Tan).

b) Tests to exclude hemolysis

Hb. 15 Gm.%. Total W.B.C. 8,300/c.mm., reticulocyte count less than 1%. The bone marrow showed no evidence of erythroid hyperplasia and the myeloid:erythroid ratio was normal. Hb. electrophoresis revealed Hb. A only. No Hb. H inclusion bodies were demonstrated. Osmotic fragility test: lysis began at 0.48% NaCl, and was complete at 0.25 NaCl. Glucose-6-phosphate dehydrogenase 145 units (normal range 100-200 units). 6-phosphogluconic acid dehydrogenase 120 units (normal range 90-180 units) and the erythrocyte glutathione reductase TPNH-linked and DPNH-linked were within the normal range.

DISCUSSION

Gilbert's disease is probably the commonest form of constitutional nonhemolytic indirect-reacting hyperbilirubinemia. The jaundice usually manifests itself in childhood but as it fluctuates in intensity and is mild it may not be observed till adulthood. It is often an incidental finding in a patient who consults a doctor for some other illness. The symptomatology is varied but gastrointestinal symptoms are common *e.g.* epigastric fullness, right hypochondrial pain, heartburn and nausea. Fatigue is particularly common in females. Quite often symptoms follow the discovery of jaundice and are related to anxiety concerning the disorder. Besides the mild icterus there are no other abnormal physical signs. Biochemically there is a nonhemolytic indirect-reacting hyperbilirubinemia with no other impairment of liver function. Liver histology is always normal.

The primary defect in Gilbert's disease has yet to be clarified fully. A hereditary factor is probably involved in some cases. Gilbert and Lereboullet (1901) in their original description used the word "familial" in the title of their paper and a study of parents and siblings of 15

patients with Gilbert's disease by Alwall et al., (1946) supports this. They observed hyperbilirubinemia in 26% of parents and 55% of siblings. More detailed studies are, however, required before the presence of a hereditary factor in this disease is established.

A deficiency in the enzyme glucuronyl transferase from the liver had been postulated by Arias and London (1957) to explain the impairment in bile excretion. However, this seems unlikely as Schiff and Billing (1959) have demonstrated that conjugated bilirubin predominates in the bile and the faecal sterocobalogen is normal. In addition satisfactory conjugation of menthol (Foult et al., 1959), salicylamide (Barniville and Misk, 1959) and N-acetyl-p-aminophenol (Schmid and Hammaker, 1959) as glucuronides has been demonstrated. In view of this, a defect in the mechanism of bilirubin transport from the plasma to its site of conjugation in the liver cell microsomes has been postulated (Schmid and Hammaker, 1959). Another factor which must also be considered is the 10 to 30 per cent of bile pigment derived from a nonhemolytic source in normal man. With (1943) has therefore suggested that this source may be responsible for the hyperbilirubinemia in Gilbert's disease.

In this patient the presence of fluctuating jaundice since adolescence, indirect-reacting hyperbilirubinemia but otherwise normal liver function and histology, no evidence of increased hemolysis and the absence of other abnormal physical signs strongly suggested a diagnosis of Gilbert's disease.

However, other common causes of hyperbilirubinemia giving an indirect van den Bergh reaction have to be excluded *e.g.* acute inflammatory disease of the biliary tract or pancreas which may give rise to transient indirect-reacting hyperbilirubinemia and hemolytic anaemia.

Indirect-reacting hyperbilirubinemia occurring during convalescence following an attack of viral hepatitis is difficult to distinguish from Gilbert's disease as clinical and laboratory findings may give little help and liver histology may be normal (Flood and James, 1947). The diagnosis of the former condition is based solely on a history of a prior acute episode of jaundice suggestive of viral hepatitis. In fact it has been postulated that post-hepatitic hyperbilirubinemia may be one variant of Gilbert's disease (Kronberg, 1942; Hult, 1950). It is therefore probable that Gilbert's disease is not a single disease entity but a syndrome caused by any one

or a combination of the above aetiological factors both constitutional and acquired. As the patient did not give a past history indicative of an attack of viral hepatitis, post-hepatic hyperbilirubinemia can probably be excluded.

The syndrome of congenital nonhemolytic hyperbilirubinemia (Crigler-Najjar type) without neurological damage has also to be differentiated from Gilbert's disease. However, the invariable presence of jaundice at birth, absence of conjugated bilirubin and the presence of neurological damage following kernicterus in some cases, help to distinguish this group.

Other familial types of chronic nonhemolytic jaundice *e.g.* Dubin-Johnson and Rotor syndromes, may easily be distinguished by the presence of direct-reacting hyperbilirubinemia and impairment in the prolonged bromsulphthalein test. Liver tissue in Dubin-Johnson syndrome also shows the characteristic brown pigmentation on microscopy.

The prognosis in Gilbert's disease is excellent but many of these patients are incapacitated through fear engendered by the incorrect diagnosis of liver disease. No specific treatment is known or needed in this disease. Confident reassurance that the vague symptoms present are not related to the icterus is all that is needed to dispel fears of hepatocellular disease that may lead to invalidism.

SUMMARY

A patient suffering from Gilbert's disease is described and the differential diagnosis discussed. The current concept of Gilbert's disease as a syndrome due to a variety or combination of defects in bile pigment metabolism, either constitutional or acquired, is put forward. Early diagnosis of the condition is necessary as reassurance will prevent undue fear and possible invalidism.

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