A yellow patient with hepatomegaly

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A 17-year-old woman, born to non-consanguineous parents, presented with 5-year history of persistent yellow discolouration of eyes and urine without any history of nausea, vomiting, pruritus, white faeces, features of hepatocellular failure and blood transfusion. On examination, she had jaundice and hepatomegaly (2 cm), soft in consistency, non-tender with smooth surface. Examination of other systems were non-contributory. At the age of 16 years, she had had an episode of acute cholecystitis and ultrasonography of the hepatobiliary system revealed cholelithiasis (figure 1) with normal hepatic echotexture, biliary system, and hepatic and common bile ducts (CBD). Other investigations revealed haemoglobin 12 g/dl, total leucocyte count $7.6 \times 10^9/l$, neutrophils 64%, lymphocytes 31%, eosinophils 5%, platelets $250 \times 10^9/l$, conjugated hyperbilirubinaemia and normal levels of serum proteins, transaminases, alkaline phosphatase and prothrombin time (table). Oral cholecystography and BSP excretion tests were not performed. The patient was managed conservatively but jaundice persisted and after 3 months she had another attack of cholecystitis. Repeat ultrasonograph showed persistence of gall stones with dilatation of upper part of the CBD. Cholecystectomy with exploration of CBD was performed. Per-operative findings demonstrated that the gall bladder was full of multiple stones but no stones were found in the CBD. Histopathology showed chronic cholecystitis with lithiasis. Liver biopsy revealed gross blackish discolouration of tissue. Microscopically, lobular architecture was preserved and hepatocytes in the pericanalicular regions were studded with blackish-brown pigment in the cytoplasm (figure 2). Some of the Kupffer cells showed similar pigment deposition. The T-tube cholangiogram done on the tenth post-operative day was normal and she made an uneventful recovery. Liver function tests 4 weeks after surgery were similar to those performed pre-operatively.

The younger sister of the patient, aged 12 years, was also found to have jaundice, hepatomegaly (2 cm), soft in consistency, non-tender with smooth surface. Her liver function tests were similar to those of the patient. Ultrasonography of her hepatobiliary system was normal, and liver biopsy was not performed. There was no jaundice in the parents and liver function tests were normal.

Figure 1 Ultrasonograph demonstrating stones in the gallbladder

Figure 2 Microphotograph showing black pigment deposition in liver parenchymal cells, concentrated in centrilobular area (H&E stain $\times 500$)

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Table Laboratory findings

Tests	Patient	Sister
Total bilirubin ($\mu\text{mol/l}$)	95.7	94.0
Conjugated bilirubin ($\mu\text{mol/l}$)	78.6	71.8
Serum protein (g/dl)	7.4	6.5
Albumin:globulin ratio	4.2:3.2	4.0:2.5
Alanine transaminase (IU/l)	40	29
Aspartate transaminase (IU/l)	35	19
Alkaline phosphatase (IU/l), normal range 37–147 IU/l	93	103
Prothrombin time (s), control value 16 s	18	17
Australia antigen (HbsAg)	negative	negative

Questions

- 1 What is the diagnosis and what disorders are associated with this syndrome?
- 2 What is the cause of cholelithiasis in this disease?

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Answers

QUESTION 1

The patient suffers from Dubin-Johnson syndrome with cholelithiasis. Certain rare associations have been observed with this disorder (box). An isolated deficiency of coagulation factor VII has been reported in a significant proportion of patients in Israel.¹ There was also a mild decrease in level of factor II and diminished prothrombin activity (< 70%) in 60% of patients. This is not due to impaired liver function as there is no hepatocellular necrosis. However, the two defects have been found to segregate independently in family studies. Another association is cholelithiasis, which was reported for the first time by Estrada-Rodriguez *et al.*²

QUESTION 2

Non-visualisation of gall bladder on oral cholecystography is found in this disorder and it is due to impaired biliary secretion of cholecystographic contrast medium. The cause of cholelithiasis is difficult to explain. It could be just an association with the disease.

Discussion

The presence of jaundice, hepatomegaly, positive family history, and conjugated hyperbilirubinaemia with normal levels of transaminases and alkaline phosphatase suggested the diagnosis of Dubin-Johnson syndrome in our case. Histopathological examination of liver tissue confirmed the diagnosis. The disorder is

Associations with Dubin-Johnson syndrome

- coagulation factor VII deficiency
- mild decrease in level of factor II
- decreased prothrombin activity (< 70%)
- cholelithiasis

transmitted as an autosomal recessive trait and the majority of patients are asymptomatic except for chronic or recurrent jaundice of fluctuating intensity.³ The cholelithiasis in the present case may be just an association or the result of the original disease process where the primary defect is impaired biliary canalicular transport of organic anions and conjugated bilirubin due to an abnormality in the membrane carrier system.⁴ Since, this benign disorder has a good prognosis with normal life expectancy, no specific therapy is required, except to treat problems like cholelithiasis. However, patients should be warned about the aggravating effect of drugs such as oestrogen-containing preparations, erythromycin, azithromycin, cloxacillin, ceftriaxone, etc, and pregnancy, on the intensity of the jaundice.

Final diagnosis

Dubin-Johnson syndrome with cholelithiasis.

Keywords: Dubin-Johnson syndrome; cholelithiasis

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