A one month old male infant presented with neonatal cholestasis and steatorrhea. Urinary bile acids and bile alcohols were elevated. Liver biopsy showed brown pigment in centrilobular hepatocytes indicative of Dubin-Johnson Syndrome (DJS). Extensive investigations ruled out known causes of cholestasis. The association of DJS and neonatal cholestasis is discussed. Bahrain Med Bull 1996;18(1):

Dubin-Johnson Syndrome (DJS) is relatively benign and rare cause of conjugated hyperbilirubinaemia. Patients are mostly asymptomatic with mild intermittent episodes of jaundice, nausea, vague abdominal pain and fatigue. Studies on experimental animal models of DJS1,2 and on membrane vesicles from human liver3 indicate the existence of at least two separate transport systems across the canalicular membrane; one for non bile acid organic anions and the other for the major bile acids.

Serum concentrations of bile acids in adults with DJS are normal. This finding has led to the speculation that the defect involves only the transport system for non bile acid organic anions such as bilirubin diglucoronide. Hence, DJS is considered as a non-cholestatic liver disease. However, the findings in our patient and the other recently reported cases of DJS syndrome and neonatal cholestasis4-8 may seem to contradict this notion. We report this case in an attempt to shed light on the association of the two conditions and to discuss the pathogenesis of the condition.

THE CASE

A one month old male infant presented with jaundice noted at day three of life. He was a product of uneventful full-term gestation and normal vaginal delivery. Birth weight was 2.7 kg. His stool was pale and greasy and his urine dark yellowish. He was otherwise feeding and thriving well. His parents were first-degree cousins. Family history was positive for sickle cell disease and G-6 PD deficiency. Two distant adult relatives have had a history of recurrent jaundice since early childhood; the aetiology of which is unknown.

Physical examination revealed a well-nourished, bright, alert and jaundiced infant. His weight, height and head circumference were at 50th percentile. He had no dysmorphic features, eye abnormalities or hypotonia. Cardiovascular
system was normal. His liver was 3 cm below right costal margin with semi firm in consistency and no tenderness. There was no splenomegaly.

Liver function tests showed a total protein of 53 g/L, albumin of 30 g/L, and globulin of 23 g/L. Total bilirubin was 224 mol/L with a direct bilirubin of 221 mol/L which gradually increased to 265 mol/L and 243 mol/L respectively. Indirect bilirubin was normal. Alkaline phosphatase was 707 IU/L, alanine aminotransferase was 90 IU/L, and gamma glutamyl transferase was 245 IU/L. Prothrombin and partial prothrombin times were normal. Other investigations showed a normal full blood count and reduced G-6 PD activity. Hepatitis and TORCH screen were negative. Urine and blood cultures were sterile. Stool culture showed no pathogens. Stool fat was high in several occasions. Pilocarpine sweat chloride iontophoresis was 20 mmol/L (0-35 mmol/L). Blood urea nitrogen and electrolytes were normal. Urine was negative for reducing substances.

Urinary cholanoids (bile acids and bile alcohols) by Fast atom bombardment - mass spectrometry (FAB-MS) showed no evidence of inborn errors of bile acid synthesis. However, the following bile acids and bile alcohols were elevated, suggesting impaired liver function: glycotrihydroxy-cholanoates, taurodihydroxycholanoates, taurotrihydroxy-cholanoates, and taurotetrahydroxycholanoates. Serum Alpha-1-antitrypsin was 1.9 g/L (normal 1.1-2.1 g/L). Urinary succinylacetone and succinylacetoacetate were within normal range.

Hepatobiliary ultrasound showed a large liver with dense texture. The gallbladder and biliary system were normal. A HIDA scan revealed a normal hepatic uptake of the radiotracer. The gallbladder was not visualised. Retention of the radioactivity in the liver and lack of excretion to the small intestine was evident up to 24 hours post-infusion.

A percutaneous needle liver biopsy was done at six weeks of age and showed a normal lobular architecture with faint brown pigment in centrilobular hepatocytes; bile ducts were normal.

At ten weeks of age, and due to the increasing jaundice and clay-coloured fatty stool the liver biopsy was repeated to exclude other causes. It also showed normal lobular architecture, normal bile ductules, and occasional giant cell transformation. Periodic Acid Schiff (PAS) stain and PAS distase (PASD) were negative for Alpha-1-antitrypsin globules. Centrilobular brown pigments were more prominent, being faintly PAS positive and diastase resistant. These granules were also positive, with Masson-Fontana stain for melanin and melanin precursors (Fig 1). Based on these findings the diagnosis of Dubin-Johnson Syndrome was made.

The patient was treated symptomatically with pheobarbital, hydrolysed formula, and vitamins A,D,E and K. Over the following three months, the patient's jaundice gradually cleared, steatorrhea improved and liver function tests returned to normal. At two years of age he was asymptomatic except for intermittent episodes of mild jaundice with intercurrent illnesses. He was thriving well with weight and height above 75 percentile.

DISCUSSION

Dubin-Johnson syndrome is a familial conjugated hyperbilirubinaemia. It is inherited as an autosomal recessive trait. The syndrome was first described in 19549,10. In adult patients symptoms are usually mild and not associated with cholestasis or liver damage.
In our patient, the findings in 99m Tc-HIDA cholescintigraphy were quite characteristic and agree with the several reported observations\textsuperscript{11,12} about the usefulness of this technique in the diagnosis of DJS.

DJS is a very rare cause of neonatal jaundice. The diagnostic lysosomal pigments are not usually evident until later in life. However, in our patient, faint brown pigment was present even at six weeks of age.

This melanin-like pigment accumulates in hepatocellular lysosomes and is responsible for the black color of the liver. The exact nature of this pigment is unknown. It is believed to be derived from epinephrine or its metabolites and ultimately from phenylalanine and tyrosine\textsuperscript{13,14}. The relationship between the pigment and the transport defect is unknown.

Knowledge about the pathogenesis of DJS has been obtained mainly from studies on animal models of human DJS: the Corriedale sheep\textsuperscript{15} and three strains of rat mutants\textsuperscript{16,17}. The defect is believed to be due to congenital impairment of an adenosine triphosphate-dependent transport system specific for a variety of multivalent organic anions, including bilirubin diglucuronide. Bilirubin is thus conjugated but not secreted into the bile due to the impairment of canalicular transport. This leads to a cellular accumulation and eventful reflux of conjugated bilirubin into the circulation.

A major difference between the rate mutants and the human with DJS, which may be of significance for the neonatal DJS with cholestasis, is the serum concentration of bile acids. It is normal in adult patients with DJS but it increases 2-5 folds in mutant rats\textsuperscript{1,16}. This is similar to the findings in two reported cases of DJS and neonatal cholestasis with elevated serum bile acids\textsuperscript{4,5}, and to what was observed in our patient, who showed an abnormal urinary bile acids pattern, indicative of impaired liver function.

The interrelationship of DJS and neonatal cholestasis in terms of cause or secondary effect is still controversial\textsuperscript{18}. The cholestasis can be a primary defect in the canalicular transport of bile acids occurring in association with the well recognised defect of DJS, which is impairment in the transport of non bile acid organic anions. However, the transient nature of the cholestasis makes the existence of a congenital persistent defect unlikely. It may result from a transient physiologic cholestasis\textsuperscript{9}, or most likely, from the cholestatic effect being secondary to the accumulation of non bile acid organic anions. This hypothesis is supported by the finding that the canalicular transport capacity for bile acids assayed in isolated membrane vesicles does not differ between rat models of DJS and control\textsuperscript{2,20}. Despite the fact that the mutant rats represent a reasonable model for human DJS, extrapolation of animal data to humans should always be viewed with caution.

In this patient, the cholestasis was transient and limited to the neonatal period, a stage in life where cholestasis is seen more often than any other period in childhood and early adult life. In addition, it is not unusual, despite the extensive investigations, not to identify the exact underlying cause of neonatal cholestasis. Accordingly, attributing cholestasis to the same primary defect in DJS seems to be an over-simplistic explanation.

**CONCLUSION**

The lack of adequate characterisation of the defect at the molecular level in the liver of human with DJS, the explanation for the role of DJS in neonatal cholestasis will remain elusive or, at best, mere speculation.

**REFERENCES**


