

DUBIN-JOHNSON SYNDROME IN A SAUDI NEONATE

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There are many disorders associated with direct hyperbilirubinemia in the neonatal period. These usually need urgent referral to identify treatable diseases. Dubin-Johnson Syndrome (DJS), which results from impaired hepatic excretory function, is an uncommon cause of neonatal jaundice and is only sporadically reported in neonates.¹ We report here a neonate who presented with direct hyperbilirubinemia in the newborn period. To the best of our knowledge, DJS has not been reported previously in neonates from Saudi Arabia.

Case Report

A baby boy was born normally at term after an unremarkable pregnancy to young Saudi first-degree cousins in a peripheral hospital. Jaundice was noticed on the third day of life. He was fed breast milk. Because of persistent jaundice for eight weeks, he was referred to the Riyadh Medical Complex (RCH) for further assessment. There was no history of perinatal stress, hemolysis or drug consumption.

On examination he was yellow with no dysmorphic features. His weight was 5.0 kg (50th percentile for age). The liver was enlarged to 4 cm below the right costal margin. The spleen was not palpable and there was no ascites. There was no skin rash, eye cataract or bleeding spots. The rest of the examination was unremarkable.

Laboratory investigation revealed a hemoglobin concentration of 83 g/L and white cell count (WIC) $11.6 \times 10^9/L$. Platelets were $530 \times 10^9/L$. Total serum bilirubin was 143 $\mu\text{mol/L}$ ($N < 34 \mu\text{mol/L}$) and direct bilirubin was 97 $\mu\text{mol/L}$ ($N < 3.4 \mu\text{mol/L}$). Serum glutamic-oxaloacetic transaminase (SGOT) was 68 U/L ($N < 55 \text{UL}$). Serum glutamic-pyruvate transaminase (SGPT) was 58

U/L ($N < 45 \text{U/L}$). Alkaline phosphatase was 702 U/L ($N < 200 \text{U/L}$). Prothrombin time (PT) was 13 seconds (control 12 seconds) and partial thromboplastin time (PTT) was 26 seconds ($N 25-37$ seconds). Urine for reducing substances and urine culture were negative. The serological screening test for toxoplasmosis, rubella, cytomegalovirus, herpes simplex virus and syphilis (TORCHS) infections were negative. Thyroid function and metabolic screen were normal.

Abdominal ultrasound revealed an enlarged liver with normal echogenicity, normal gallbladder and normal spleen. $^{99\text{m}}\text{Tc}$ -labelled diisopropyl imino diacetic acid (DISIDA) scan study showed good uptake with delayed excretion of isotope to the intestine. The liver tissue obtained by percutaneous liver biopsy was dark greenish in color and histopathology study confirmed the diagnosis of DJS (Figures 1 and 2). A Bromsulphalein (BSP) test was not done.

The patient was discharged in good condition. He had good weight gain, a decreased level of bilirubin, and normal liver enzymes one month after discharge.

Discussion

DJS, which was described in 1954, is an uncommon hereditary disease. It occurs most frequently among the Iranian Jews, with a prevalence of 1:1300.¹ The transmission has been mostly described as autosomal recessive, but an autosomal dominant mode has also been reported. About one-third of patients have a positive family history.²

Our patient presented with jaundice in the neonatal period, which persisted for three months. Several cases of neonatal jaundice due to DJS have been reported in the international literature,^{3,4} mostly with mild jaundice, but one case was reported to have severe cholestasis.⁴ Usually DJS presents with recurrent jaundice in older children or adults. These may be induced by surgery, intercurrent infections, vigorous physical exercise, or contraceptive pills.² Total plasma bilirubin ranges from 30 to 90 $\mu\text{mol/L}$. Symptoms like abdominal pain, nausea,

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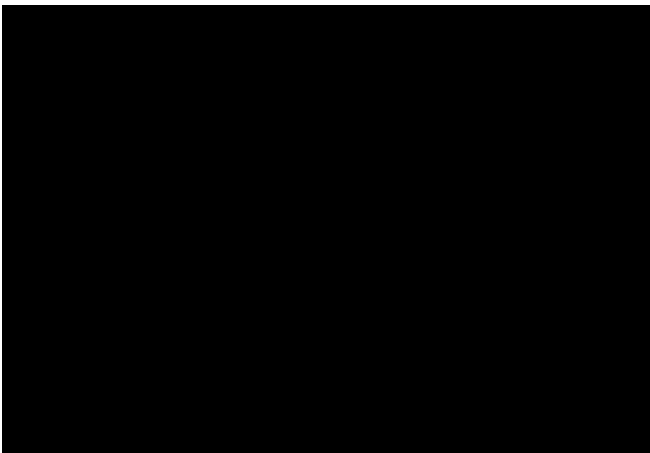


FIGURE 1. Liver biopsy showing the Dubin-Johnson (lipofuscin-like) pigment in hepatocytes (hematoxylin and eosin stain, 250x).

anorexia, diarrhea and weakness were also common complaints by most of the older patients.^{1,2} Pruritis is rare compared to other causes of conjugated hyperbilirubinemia (CHB).¹ For unknown reasons, these patients stay free of jaundice for years after the neonatal period.

The diagnosis is usually made by the clinical features, characteristic curve of BSP, abnormal liver, ^{99m}Tc DISIDA scan and typical histology of the liver. We believe that diagnosis could be made to a high certainty without the BSP test.⁵

Physiologically, the bilirubin is taken up by the hepatocytes against the concentration gradient from albumin bilirubin complex in the blood. After the bilirubin is conjugated to bilirubin diglucuronide in endoplasmic reticulum, it is excreted by the liver cells into the bile canaliculi. In DJS, the defect is in the excretion of normally conjugated bilirubin into bile canaliculi, which leads to retention of bilirubin within hepatocytes and subsequent reflux from hepatocytes back into circulation.

The BSP test could confirm the diagnosis and is dealt with by the hepatocytes in the same way as bilirubin.³ After the immediate peak, the hepatocytes take up the dye normally and the level declines. But when the conjugated dye starts refluxing back from hepatocytes into the blood, the second peak appears around 90 minutes onwards. In normal subjects, no second peak is seen. In Rotor syndrome, which has a similar excretion defect, the initial fall is not as marked and the level stays higher in the blood for a longer duration. Unfortunately the BSP is not available in RCH.

A recent increase in the 24-hour urinary proportion of coproporphyrin Isomer I to Isomer III is highly characteristic of DJS. Isomer I can reach as high as 80% of total coproporphyrin. Coproporphyrins are formed



FIGURE 2. Liver biopsy showing the black DJS pigment in hepatocytes (Masson-Fontana stain, 250x).

within the body fluid during heme biosynthesis in two isomers: Isomer I, a product of heme catabolism, and Isomer III, a heme precursor. Normally, the Isomer I-to-Isomer III ratio is 1 to 3-4. In other causes of CHB, the Isomer I reaches a maximum of 65% of total coproporphyrin. The mechanism for this reversal ratio is not well understood.⁶ The liver in DJS shows good uptake of the ^{99m}Tc DISIDA and gives good visualization of the liver. Due to defective excretion, the liver stays more intense for a longer time, so the gallbladder and bile ducts may not be seen. There is delayed excretion of the tracer to the intestine and a large proportion of it is excreted through the kidneys. This occurs despite the presence of bile in the intestine. These features were seen in our patient and are considered diagnostic for DJS.^{2,7}

The typical dark brown pigment which is visualized as coarse lipofuscin-like hepatocellular granules accumulates in the lysosomes of hepatocytes.³ These were seen in our eight-week-old patient and they were noticed at an earlier age in a previous case report.⁸ Their presence was taken as a definitive for DJS diagnosis.⁸ They are recognized by characteristic black pigment with Masson-Fontana stain. Electron microscopy reveals coarse, iron-free pigment within the lysosomes. It has been demonstrated that there is adenosine triphosphate (ATP) dependent transport mechanism responsible for excretion of bilirubin diglucuronide and other organic anions, as well as metabolites of aminoacids like phenylalanine, tyrosin and tryptophan. So the end products of these aminoacids are normally excreted as metanephins.⁹ In DJS, this transport mechanism is defective and these end products are converted into lysosomal pigment which are different than melanin. It is shown that viral hepatitis causes complete disappearance of pigment with subsequent slow reaccumulation.³

In experimental animals, the renal histopathology study revealed glomerular lesions with mesangial expansion and

proliferation. Furthermore, microhistopathological studies showed renal changes like IgA nephropathy, but such changes have not been described in humans.¹⁰

The prognosis of DJS is excellent despite recurrent hyperbilirubinemia events. Usually therapy is not required, but if jaundice is severe enough, phenobarbitone has been found effective.^{3,4}

Neonatologists, pediatricians and family physicians need to be aware of this benign disease when they come across neonates or infants with direct hyperbilirubinemia. Unnecessary worry can be avoided by correct diagnosis.

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