Case Report

Pregnancy with Dubin Johnson Syndrome – A case report

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Abstract
Dubin Johnson Syndrome is an autosomal recessive benign disorder of bilirubin metabolism, in which patients have icterus with non pruritic conjugated hyperbilirubinaemia. Condition may get aggravated during pregnancy and result into fetal wastage. A case is reported in which young primigravida presented with severe anaemia, icterus and conjugated hyperbilirubinaemia. She had premature delivery at 30 weeks of gestation. There were no maternal peripartum complications. She was treated with blood transfusion and supportive treatment. Her liver functions returned back to normal within short period after delivery. Conditions like Dubin Johnson syndrome must be kept as differential diagnosis while dealing with cases of jaundice in pregnancy.

Keywords: Dubin Johnson Syndrome, Jaundice in Pregnancy, Unconjugated hyper-bilirubinaemia

1. Introduction
Dubin-Johnson syndrome is an inherited, relapsing, benign disorder of bilirubin metabolism. This rare autosomal recessive condition is characterized by conjugated hyperbilirubinemia with normal liver transaminases, a unique pattern of urinary excretion of heme metabolites (coproporphyrins), and the deposition of a pigment that gives the liver a characteristic black color. Patients with Dubin-Johnson syndrome tend to develop nonpruritic jaundice during their teenage years. The overall prevalence of Dubin-Johnson syndrome is extremely low. Dubin-Johnson syndrome has been described in all nationalities, ethnic backgrounds, and races. The highest recognized prevalence of the disease (1 case per 1300 population) is in Iranian Jews and is clustered in the same families. This group may have an associated deficiency in clotting factor VII that is not observed in other populations. The prevalence in Moroccan Jews is nearly as high, a reflection of the fact that these populations diverged about 2000-2500 years ago.

2. Case Report
Twenty one years unbooked primigravida from lower socio economic class, labourer by occupation referred from private practitioner as a case of eight months pregnancy with severe anaemia. Patient gave history of pain in abdomen and increased frequency of stools since 8 days. Stools were watery with frequency of 5-6 times a day and were black in colour. She was admitted in a private hospital and was referred from there, as she did not respond to treatment. Patient had brought her recent laboratory investigations which showed severe anaemia and hyper bilirubinemia.

Her obstetrical and menstrual history revealed that she was married two years back with first degree consanguinity. She was primigravida with gestational age of 32 weeks. She had normal menses in the past. She had not received any antenatal care and had not taken any haematinic tablets. Patient gave history of yellowish discoloration of sclera since childhood and recurrent episodes of jaundice since childhood for which she received ayurvedic medicines. She was not admitted for this problem in the past. She did not have fever or itching over skin in the past. During present pregnancy, she had two episodes of jaundice for which she had taken only oral ayurvedic medicines. Before present illness, her sleep and appetite was normal with normal regular bowel habits. She was not addicted to tobacco (in any form) or alcohol. No other member from her family had similar presenting complaints. She was living in kuchha house with poor sanitary and drinking water facilities.

On examination, she was thin built woman, conscious, oriented, afebrile with pulse rate of 100/minute and blood pressure of 150/78 mmHg. Her respiration was normal. There were signs of dehydration. She had gross pallor and icterus. There was yellowish discoloration of skin. There was no lymphadenopathy or oedema over feet. Her cardiovascular examination revealed tachycardia. Respiratory system on auscultation was normal. Obstetric examination revealed that the height of uterus was 28 weeks. Uterine tone was raised. The baby was in cephalic presentation with fetal heart rate of 140 beats /minute. Upper abdominal palpation revealed mild hepatomegaly and gross spleenomegaly. Per vaginal examination revealed that she was in latent phase of preterm labour.

Blood examination showed Haemoglobin level of 4.5grams/dl, Total leucocyte count of 6636/cumm, Platelet count of 88,000 /cumm, Packed cell volume was 15%. There was marked aniso-pokilocytosis. Peripheral blood smear showed marked hypochromia and microcytosis. Few tear drop cells and macrocytes were seen with mild polychromasia. There were no hemo parasites. Her prothrombin time (PT) and APTT values were normal. Blood indices like MCV, MCH, MCHC and RDW were suggestive of iron deficiency anaemia. Renal function tests showed blood urea of 45.9mg%. Liver function tests showed grossly abnormal function with total bilirubin value of 20.5mg%, Conjugated bilirubin value of 9.7mg%. Serum levels of AST, ALT and Alkaline phosphate were normal. She had raised S.LDH values of 1345 IU /l. Total Blood protein level was 6.5gm. S. Albumin level was 2.7 gms and S. Globulin level was 3.8gm%. Her blood tests for hepatitis, syphilis, HIV, Malaria and Dengue were normal. Her urine and stool microscopy examination was normal. Tests for sickle cell anaemia were normal. Haemoglobin electrophoresis sample was given after she had received two units of blood transfusion. HbF values were 19%. Ultrasonography of abdomen showed gravid uterus with 29 weeks fetus with anhydramnios. Liver span was 17cms with normal portal vein and common bile duct. There were
no focal lesions in hepatobiliary system. Gall bladder showed sludge in its lumen. The wall thickness was normal and there was no calculus. There was gross splenomegaly measuring 20 cms.

Patient was treated with intravenous fluids, Blood transfusion, inj. Cephotaxime, Inj. Metrogyl, intravenous vitamin B complex and other supportive treatment. Her vitals were monitored.

Patient had premature delivery on second day of admission. There was no intrapartum or immediate postpartum complication. The baby had very low birth weight (1150 grams) and had features of intrauterine growth restriction. Baby was kept in intensive neonatal care unit on oxygen by mask, intravenous fluids and prophylactic antibiotics. Baby had respiratory distress syndrome.

Patient had rapid improvement after delivery. There was rapid and progressive reduction in serum bilirubin neonatal levels after delivery. (Table 1) The sclera became white in five days time and the yellow discoloration of the skin disappeared. (Fig.1 and 2)

Table 1: Showing rapid improvement in biochemical parameters in the case of Dubin Johnson Syndrome

<table>
<thead>
<tr>
<th>Days From admission</th>
<th>Total Bilirubin (mg/dl)</th>
<th>Conj. Bilirubin (mg/dl)</th>
<th>S.LDH (IU/L)</th>
<th>Haemoglobin (gm %)</th>
<th>Platelet count (thousand/µl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20.5</td>
<td>9.70</td>
<td>1343</td>
<td>4.5</td>
<td>88</td>
</tr>
<tr>
<td>2</td>
<td>26.3</td>
<td>11.50</td>
<td>1264</td>
<td>6.7</td>
<td>84</td>
</tr>
<tr>
<td>4</td>
<td>8.60</td>
<td>4.30</td>
<td>1247</td>
<td>8.3</td>
<td>150</td>
</tr>
<tr>
<td>8</td>
<td>5.50</td>
<td>2.20</td>
<td>490</td>
<td>10.4</td>
<td>264</td>
</tr>
<tr>
<td>12</td>
<td>3.50</td>
<td>2.00</td>
<td>372</td>
<td>9.8</td>
<td>324</td>
</tr>
</tbody>
</table>

Patient was not ready to stay in hospital after 15 days of hospitalization for personal reasons. She was discharged on persistent request. She was advised to come for follow up after two weeks.

3. Discussion

Dubin-Johnson syndrome is an autosomal recessive disorder that is caused by a mutation in the gene responsible for the human canalicular multispecific organic anion transporter (cMOAT) protein, also called the multidrug resistance protein 2 (MRP2) or ABCC2. This protein mediates adenosine triphosphate (ATP)-dependent transport of certain organic anions across the canalicular membrane of the hepatocyte. Dubin-Johnson syndrome occurs in both sexes, but some authors have reported increased incidence and earlier onset in males. It is rarely detected before puberty, although neonatal cases have been reported. It is most often diagnosed in the late teens and early adulthood.

The conjugated hyperbilirubinemia observed in Dubin-Johnson syndrome results from defective transport of bilirubin glucuronide across the membrane that separates the hepatocyte from the bile canalculi. Pigment that is not secreted from the hepatocyte is stored in the lysosome and gives rise to black colour to liver. A hallmark of Dubin-Johnson syndrome, the mechanism of which is not fully understood, is a reversal of the usual ratio between the byproducts of heme biosynthesis: urinary coproporphyrin I levels are higher than coproporphyrin III levels. In unaffected individuals, the ratio of coproporphyrin III to coproporphyrin I is approximately 3-4:1.

Laboratory studies reveal conjugated hyperbilirubinemia, with total bilirubin serum levels usually in the 2- to 5-mg/dL range (but potentially as high as 25 mg/dL). In patients with elevated conjugated bilirubin levels but otherwise normal liver function findings, the diagnosis of Dubin-Johnson syndrome can be confirmed by demonstrating an increase in the ratio of urinary coproporphyrin I to coproporphyrin III; type I makes up 80%, rather than the usual 25%, of the urinary coproporphyrin content in these patients. Patients with Dubin-Johnson syndrome tend to have unique findings on hepatobiliary scintigraphy scans, demonstrating a combination of intense and prolonged visualization of the liver and delayed or failed visualization of the gallbladder.
Dubin-Johnson syndrome is a benign condition, and life expectancy among patients is normal. Complications of Dubin-Johnson syndrome include jaundice (the most consistent finding) and hepatomegaly. Oral contraceptives, pregnancy, and intercurrent illness may exacerbate jaundice. Reduced prothrombin activity, resulting from lower levels of clotting factor VII, is found in 60% of patients. Some neonates present with cholestasis, which may be severe. Increased fetal wastage was reported in one study. In a case report, cholecystolithiasis and choledocholithiasis developed in the presence of Dubin-Johnson syndrome. It requires no specific therapy, although patients should be warned that pregnancy, oral contraceptive use, and intercurrent illness can exacerbate the associated jaundice. Once diagnosed with Dubin-Johnson syndrome, patients should be informed of the disease process and its benign nature, and they should understand that no further investigative workup is required in the future.

The present case was from very poor socio economic background and was illiterate. She was not having any major symptom and thus had not taken any consultation from physician in the past. In this part of the region, many people believe in treating jaundice with some non allopathic medication or therapies, many of which have no scientific basis. The diagnosis of Dubin Johnson syndrome was made on the basis of history of onset since childhood with repeated attacks of jaundice without pruritis and high levels of conjugated bilirubin without evidence of obstruction in hepato-biliary tract. Additional confirmatory tests could not be carried out as the facilities were not available in this hospital and patient was not able to undergo these tests due to financial reasons.

4. Conclusion

Dubin Johnson syndrome is a rare cause of jaundice during pregnancy. It is diagnosed from history of onset during childhood and presence of conjugated hyper bilirubinaemia. It has a benign course but can get aggravated during pregnancy, as it has happened in this case. The fetal outcome may be unfavourable in the presence of other associated adverse factors.

References