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Dubin-Johnson syndrome: A rare case report

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ABSTRACT

Dubin-Johnson syndrome is an inherited metabolic disorder in which the primary defect is in the MRP2 protein, which leads to an overflow of conjugated bilirubin in the blood leading to hyperbilirubinemia. It is a benign disorder that develops from a genetic defect in bilirubin pigment secretion that causes persistent jaundice and conjugated hyperbilirubinemia. Multiple cases of hyperbilirubinemia disorders similar to Dubin-Johnson syndrome were reported, but each varies in the levels of conjugated bilirubin and its response to the treatment. This syndrome's clinical cases are often misdiagnosed and mistreated as mostly the affected individuals are asymptomatic. In this clinical case report, a 23-year-old female patient was admitted to the hospital with chief complaints of recurrent jaundice and abdominal pain. Additional examination and testing revealed that she had been jaundiced from birth and had a family history of the same. She was managed conservatively and follow-up revealed a good prognosis. This article describes a case of Dubin-Johnson syndrome that is incredibly unusual. However, the patients have an average life expectancy and don't require any therapy.

Keywords: Dubin Johnson Syndrome, Hyperbilirubinemia, MRP2 protein, Conjugated bilirubin.

1. INTRODUCTION

Dubin-Johnson syndrome, also known as black liver disease, is a rare disease which is autosomal recessive in inheritance. It is a benign liver disease, which is characterized by conjugated hyperbilirubinemia (which can be chronic or intermittent) and recurrent jaundice. It is insidious in onset. The underlying mechanism is a mutation of the ABCC2 gene (Wu et al., 2021). The first case of Dubin-Johnson syndrome was diagnosed in 1954 by Dubin and Johnson. This syndrome often presents as a missed diagnosis of neonatal cholestasis. The gold standard test for diagnosis of this test is liver biopsy. Other tests done are hepatobiliary iminodiacetic acid (HIDA) scan, bromsulphalein test and cholecystography (Kamal et al., 2022).

The syndrome is due to a defect in the expression of the multidrug resistance protein 2 (MRP2). Molecular testing reveals a mutation of the ABCC2 gene, which affects bile transportation and secretion, which is the syndrome's pathogenesis (Kuo et al., 2010). The majority of Dubin-Johnson syndrome patients live normal lives with asymptomatic hyperbilirubinemia

and mild jaundice. Mild jaundice is sometimes the only clue leading to a diagnosis of this syndrome. Sometimes it may be associated with cholelithiasis, in which the patient usually presents with colicky pain (You et al., 2021).

If liver function tests in people who have experienced mild jaundice several times from childhood only reveal elevated serum bilirubin levels and no abnormalities in the liver enzymes, finding out if hyperbilirubinemia is conjugated or unconjugated is the next step in the inquiry. Peripheral blood counts and reticulocyte counts are done in the case of the former. If it is positive, the patient is examined for haemolytic disorders, but if negative, the potential for Gilbert's syndrome is raised. Conjugated hyperbilirubinemia increases the probability of Rotor's syndrome and Dubin-Johnson syndrome. Dubin-Johnson syndrome has been discovered to have abnormal coproporphyrin excretion and in some instances, factor VII insufficiency (Nisa and Ahmad, 2008; Yasawy et al., 1988).

Anorexia, diarrhea, weakness, nausea and unexplained stomach pain are reported by almost 80% of the patients. Along with this, their complaints can falsely lead to the diagnosis of viral hepatitis. The findings of the bromsulphalein test are indicative of Dubin-Johnson syndrome. Following a decrease in the serum level of bromsulphalein, the dye concentration rises two times. Bromsulphalein second increase results from the dye's reflux from the hepatocytes into the plasma (Yasawy et al., 1988).

2. CASE PRESENTATION

A 23-year-old female came to the hospital with the chief complaint of recurrent jaundice since childhood. Jaundice was mild and intermittent in nature. The patient also had a history of abdominal pain and it was generalized in nature, predominantly in the upper right quadrant of the abdomen. The patient also gave a history of the consumption of oral contraceptive pills. The patient looked anxious at the time of the history collection and there was no history of fever, nausea and vomiting.

On physical examination, the patient's body color was pale yellow and icterus was present. Her urine was dark yellow in color and the stool color was brown. On history collection, the patient's family had a similar history of the disease. The patient had a previous test report with similar elevated conjugated bilirubin levels. An impression of conjugated hyperbilirubinemia and a diagnosis of Dubin-Johnson syndrome were made.

On examination, all her vital signs were normal. The patient’s investigations revealed raised total bilirubin level of 48μmol/L. The direct conjugated bilirubin was elevated (31μmol/L). Aspartate aminotransferase was found to be 26U/L and alkaline phosphatase was 170U/L. The reticulocyte count was 1.5%. Urine bilirubin was 1.2 mg/dl. The serological test for hepatitis A and B was negative. Values of all laboratory tests have been summarized in (Table 1).

Table 1 Laboratory tests. Total serum bilirubin, direct conjugated bilirubin and urine bilirubin were elevated

Sr. No.	Laboratory tests	Observed Values	Normal Values
1	Total Serum Bilirubin	48μmol/L	1.71-20.05μmol/L
2	Direct Conjugated Bilirubin	31μmol/L	<5.1μmol/L
3	Aspartate aminotransferase	26U/L	<38U/L
4	Alkaline Phosphatase	170U/L	<500U/L
5	Reticulocyte count	1.5%	0.5% - 2.5%
6	Urine Bilirubin	1.2mg/dl	0.3-1.0mg/dl

Ultrasonography exhibited normal liver without any biliary obstruction and no organomegaly. All other liver function tests were within normal limits. The liver biopsy of this patient shows deposition of pigment melanin leading to black liver (Figure 1).

Based on the history, clinical features, examination and laboratory investigation a confirmed diagnosis of Dubin-Johnson syndrome was made. There is no known treatment for this syndrome so symptomatic treatment, drug therapy, including Rifampicin 600mg and Ursodeoxycholic acid (UDCA) 300mg for hyperbilirubinemia, was started. For abdominal pain, ibuprofen 400mg was prescribed. Vitamin K supplementation was recommended. After a month of treatment, she was asked to repeat the liver function tests, which showed a reduction in the conjugated bilirubin levels to 29μmol/L in a month. The patient was suggested to visit their specialist after a month to assess the effectiveness of the medication. She was also counseled on genetic and lifestyle modifications.

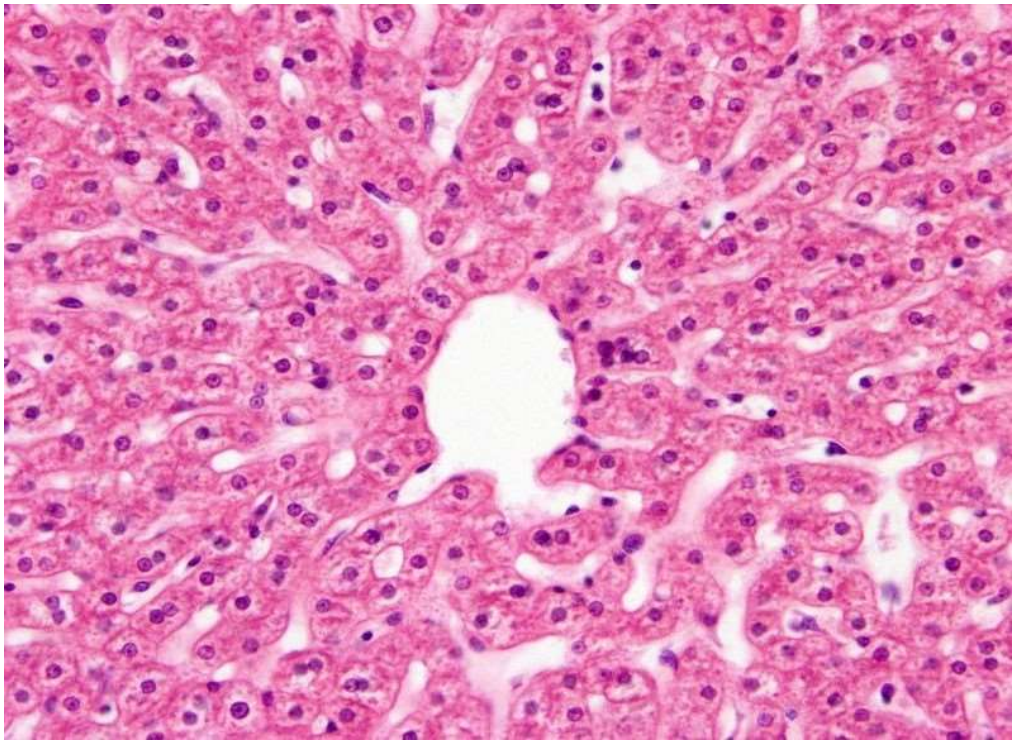

Figure 1 Liver biopsy (40X) showing deposition of pigment melanin. Arrows show the characteristic histopathology finding of Dubin-Johnson syndrome

3. DISCUSSION

Dubin-Johnson syndrome is a benign hereditary condition that causes conjugated hyperbilirubinemia, which was first discovered by Dubin, Johnson, Sprinz and Nelson in 1954. Except for select groups of Jews, where the prevalence reached one in 1300, it is an uncommon disorder (Kuo et al., 2010). Both sexes have equal chances of having Dubin-Johnson syndrome. One-third of those who have this syndrome have a similar history. Intermittent and recurrent jaundice since birth is the main presenting complaint of the patients. Jaundice is persistent in nature and varies in severity. Stress, alcohol, infection, pregnancy, oral contraceptive pills and surgery can all worsen it (Yasawy et al., 1988).

Pediatric Dubin-Johnson syndrome patients with MRP2 abnormalities experience clinical jaundice, direct bilirubin elevation, cholestasis and hepatocyte damage and increased liver enzymes (You et al., 2021). Dubin-Johnson syndrome individuals have a metabolic abnormality from birth, but it rarely manifests in infancy and typically only gets worse in late adolescence. Doctors should consider the potential of diagnosing Dubin-Johnson syndrome if cholestasis is found in healthy-appearing newborns and infants who undergo a routine physical examination and have normal hepatocytes and biliary enzyme levels. In those patients, a high index of suspicion for Dubin-Johnson syndrome helps avoid needless extensive, expensive and intrusive testing. The confirmatory diagnosis is made by molecular genetic testing of the ABCC2 gene (Kamal et al., 2022).

The reduced release of bile acids into the bile may be the cause of cholelithiasis. A patient with Dubin-Johnson syndrome and cholesterol gallstones was described by Yehuda and colleagues. They examined the patient's bile composition and discovered a high lithogenic index. There are a few case reports of Dubin-Johnson syndrome and cholelithiasis being diagnosed and treated at the same time in the literature (Kuo et al., 2010). In this case report, the patient presented with recurrent jaundice and abdominal pain in the upper right quadrant of the abdomen. The diagnosis was made based on a detailed history and examination and to confirm the diagnosis liver biopsy was done. The biopsy result revealed a dark brown pigment in hepatocytes.

Due to the widespread buildup of coarsely granular pigment, which is brown in colour in the cytoplasm of hepatocytes, the liver appears grossly grey to black in colour; hence the reference to the darkly pigmented liver (Nisa and Ahmad, 2008). Iron in states of iron overload (Perl's stain positive) and lipofuscin (periodic acid-Schiff (PAS) positive) are the critical differential diagnoses for liver biopsies with dark pigment (Nisa and Ahmad, 2008).

The MRP2 gene is encoded by the ABCC2 gene, which is found on autosomal 10q24. An increasing number of Dubin-Johnson syndrome patients have been detected by genetic testing since identifying the gene mutation that causes the disease in 1997. The primary transporter of bilirubin is MRP2. Therefore, bilirubin excretion abnormalities might result from aberrant MRP2 expression

or functional damage. MRP2 abnormality may impair bile flow and result in cholestasis. Studies have demonstrated a connection between the ABCC2 gene mutation in patients with this syndrome and the loss of MRP2 function, which may result in hyperbilirubinemia (You et al., 2021).

A deficiency in the MRP2 gene may cause MRP2 mRNA to degrade quickly, MRP2 protein to be unstable, MRP2 synthesis to degrade protein and the MRP2 protein's inability to be sorted. The MRP2 gene is also known as the canalicular multi specific organic anion transporter (cMOAT) as it serves as an export pump in hepatocytes. The molecular cause of this illness has been determined to be a deficiency in the canalicular membrane of hepatocytes. It manifests as a failure to transfer additional anionic conjugates into the biliary flow in addition to a reduction in the secretion of conjugated bilirubin (Kuo et al., 2010).

As epigenetic and genetic research and sequencing technology advance, complicated illnesses become more prevalent. Patients with Dubin-Johnson syndrome have been shown to have ABCC2 mutations such as missense and nonsense mutations, gene deletion and site mutations. The clinical diagnosis of seven Dubin-Johnson syndrome patients in China was previously examined and it was discovered that the patients had at least one non-synonymous mutation in the ABCC2 gene (Wu et al., 2021). Only two individuals exhibited complicated heterozygous mutations, whereas all detected mutations were heterozygous, indicating the involvement of additional clinically significant ABCC2 gene mutation.

Two studies from Saudi Arabia were published: One contained a large collection of 28 Dubin-Johnson syndrome cases with genetic proof and the other contained one instance without any proof. Dubin-Johnson syndrome patients have a metabolic abnormality since birth; however, it seldom manifests in infancy and typically becomes more noticeable in late adolescence (Kamal et al., 2022). Dubin-Johnson syndrome typically has minor clinical signs and a good prognosis. The patients have raised total serum bilirubin levels, specifically the direct conjugated bilirubin, indicating jaundice like in this case report. The liver biopsy of patients reveals a characteristic finding of Dubin-Johnson syndrome, which is the deposition of melanin pigment in the hepatocytes. In this case report, there is no similar family history, unlike the other cases that have a family history of this syndrome (You et al., 2021).

4. CONCLUSIONS

Dubin-Johnson syndrome is an uncommon genetic disorder the diagnosis of which is a significant difficulty for the doctor. However, the illness can be identified with a comprehensive history, particularly the family history, clinical findings and laboratory investigations. For a specific diagnosis, genetic testing needs to be done necessarily. A multifaceted strategy for management is a must and it entails counseling for lifelong food change, ensuring adequate hydration and avoiding triggers like stress, alcohol and pregnancy. Along with routine follow-up, genetic counseling is a crucial management component, particularly concerning consanguinity. Presently, there is no specific treatment for Dubin-Johnson syndrome. The treatment is conservative. However, it is necessary to create treatments that target particular gene alterations and mutations.

Contribution of the Authors

Uniform contributions have been put into the study by each author.

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Informed Consent

The procedure along with the risk involved was thoroughly explained to the patient before the onset of the procedure, Written & Oral informed consent was obtained from the participant.

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Conflict of interest

The authors declare that there is no conflict of interests.

Data and materials availability

All data sets collected during this study are available upon reasonable request from the corresponding author.

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