Steatohepatitis Coexisting with Dubin Johnson Syndrome: A Case Report

Mehmet Ali Erdogan[1], Yahya Atayan[1], Yasir Furkan Cagin[1], Yilmaz Bilgic[1], Murat Aladag[1], Murat Harputluoglu[1], Yuksel Seckin[1], Aysen Bayrac[2], Emine Samdancı[3]

[1] Department of Gastroenterology, Faculty of Medicine, Inonu University, Malatya, Turkey

[2] Department of Internal Medicine, State Hospital, Agri, Turkey

[3] Department of Pathology, Faculty of Medicine, Inonu University, Malatya, Turkey

Abstract

Dubin-Johnson syndrome (DJS) is a benign autosomal recessive liver disorder characterised by an intermittent jaundice caused by chronic and conjugated hyperbilirubinaemia. Many mutations in multidrug resistance associated protein (MRP-2) gene have been identified in patients with DJS. Although the disease is usually asymptomatic, some patients may experience vague abdominal pain. In this report, we present a patient with steatohepatitis diagnosed as DJS through a liver biopsy. The patient, 38 years of age, male was admitted to our clinic with vague abdominal pain and jaundice. High levels of serum transaminase, triglyceride, cholesterol and bilirubin were found. Ultrasonography showed Grade II hepatosteatosis in the liver. When steatohepatitis and intracytoplasmic dPAS positive pigment which is more prominent in the perivenular region (zone 3) was observed in the liver biopsy, the patient was diagnosed as DJS coexisting with steatohepatitis.

Key Words: Dubin-Johnson syndrome, steatohepatitis, hyperbilirubinaemia

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Corresponding Author*:* Mehmet Ali Erdogan, Department of Gastroenterology, Faculty of Medicine, Inonu University, 44280, Malatya, Turkey
E-mail: Mehmet_ali_erdogan@hotmail.com
Phone: +90 422 341 0660-4112 **Fax:** +90 422 341 0036

Introduction

Dubin-Johnson syndrome (DJS) is a benign and chronic disorder characterised by a intermittent jaundice caused mostly by chronic and conjugated hyperbilirubinaemia. Although patients are frequently diagnosed during their early adolescence or early adulthood, case reports between 2.5 month old and 63 years old patients are present [1]. This manifestation is an autosomal recessive syndrome characterised by selective disorder of excretion of conjugated anions into the bile canaliculus. However, excretion of bile acid into the bile is normal in patients [2].

Although pathologic features of non-alcoholic fatty liver disease (NAFLD) are similar to those of alcoholic liver damage, these findings can also be found in individuals who do not consume alcohol. NAFLD encompasses a spectrum of abnormal liver histology ranging from simple steatosis to nonalcoholic steatohepatitis and cirrhosis [3]. Although the most frequently seen risk factors for non-alcoholic steatohepatitis (NASH) are Type II Diabetes Mellitus, obesity and hyperlipidemia; female gender, TPN (total parenteral nutrition), ileal by-pass and some drugs are other risk factors [4].

In this report, we aimed to present a patient with jaundice and vague abdominal pain, who is diagnosed as NASH and DJS.

Case

38 years old male patient complaining from abdominal pain and intermittent jaundice admitted to our clinic. The patient had a history of a gallbladder surgery. He has not drunk any alcohol. Vital signs during physical examinations: fever was 36.9°C, pulse rate was 98 beat/min, blood pressure was 115/75 mmHg and respiratory rate was 17/min. Body mass index: 26 kg/m^2. The patient was conscious, cooperative and oriented. Mild icterus in the sclera was observed. On the abdominal examination, we detected mild sensitivity on the right upper quadrant. No hepatosplenomegaly was observed and other physical examination findings were normal.

Laboratory findings of the patient: Hemoglobin 16.1 g/dL, white blood cell 8600 /mm^3, thrombocyte 381000 /mm^3; alkaline phosphatase 40 U/L, gamma glutamyl transpeptidase 61 (GGT) U/L, aspartate aminotransferase (AST) 44 U/L, alanine aminotransferase (ALT) 87

U/L, amylase 66 U/L, lipase 24 U/L, lactate dehydrogenase 315 U/L, triglyceride 441 mg/dL, cholesterol 269 mg/dL, LDL cholesterol 144 mg/dL, HDL cholesterol 37 mg/dL, total bilirubin 8.3 mg/dL, direct bilirubin 5.28 mg/dL, albumin 3.9 g/dL, prothrombin time was measured as 12.2 sec and other laboratory findings were normal. Elisa test results were HBsAg (-), AntiHBs (-), AntiHBc total (-), Anti HCV (-), Anti HAVIg G (+) and Anti HAVIgM (-). Autoimmune markers were: ANA (-), ASMA (-), LKM1 (-), and AMA (-). Hemolysis symptoms were not observed. Abdominal ultrasonography revealed a Grade 2 increase of liver echogenity, and the spleen and liver sizes were normal. The gallbladder found to have undergone a surgery. Intrahepatic and extrahepatic bile ducts were normal. In magnetic resonance cholangiography, bile ducts were observed to have normal anatomical appearance and signal intensity. In the light of all these findings, the patient was thought to have steatohepatitis. However, the fact that the level of bilirubin is high, the liver is not in cirrhotic stage and icterus has been present since childhood, it was though the patient could have hereditary conjugated hyperbilirubinaemia and as the best approach for both diagnoses, a liver biopsy was performed.

In the liver biopsy: Steateatohepatitis, intracytoplasmic dPAS positive stain more prominent in the perivenular region (zone 3) and fibrosis 1/4 (perisinusoidal mild) were found (Figures 1-3). Based on the histopathological findings and the results of examinations and tests, the patient was diagnosed as DJS and NASH.

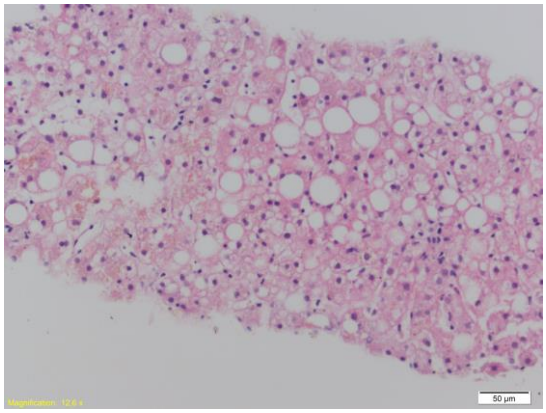

Figure1. Prominent dark brown granular pigment in the hepatocytes. H&E x400

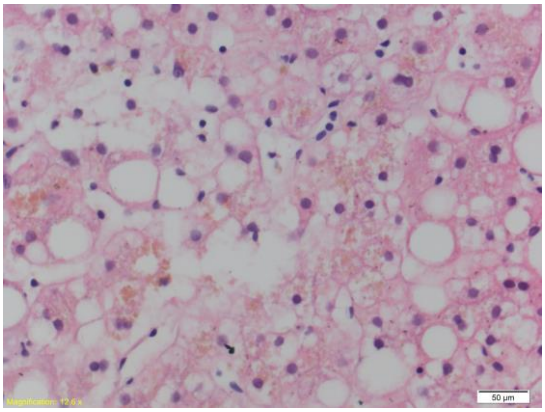

Figure 2. The pigment is stained with DiPAS. DiPAS x400

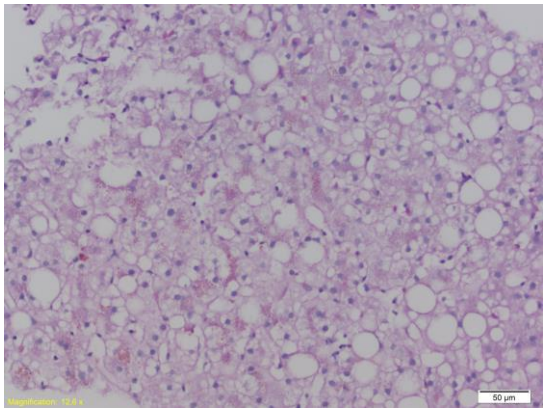

Figure 3. Reticulin staining x100

Discussion

Although the disease is generally asymptomatic, patients may rarely have symptoms such as mild upper quadrant pain, weakness, nausea and vomiting. Total bilirubin level is mostly around 2-5 mg/dL. However, this level can sometimes rise to 20-25 mg/dL. Although hepatomegaly was reported very rarely, liver function tests including bile acids are completely normal [5].

In patients with DSJ, many mutations on ABCC2 gene that codes MRP2 located on the chromosome 10q4 have been identified. First of these mutations has been described in 1997. MRP2 gene is the ATP dependent canalicular transport protein. When function of this gene lost, excretion of organic anions and conjugated bilirubin into bile is disrupted [6].

In patients with DJS, histology shows deposition of black pigment in hepatocytes and accumulation of melanin-like black pigment in lysosomes under electron microscope. Radiologic examinations also reveal decrease of or complete disruption in excretion of anionic contrast materials [7-8]. Determining of urinary isomers is another approach used in diagnosing DJS. In normal human urine, it is seen as coproporphyrin III level > coproporphyrin I level; but in patients with DJS the ratio of coproporphyrin I to the total coproporphyrin is 50% in heterozygotes and 80% in homozygotes [9].

DJS may also associated with hepatobiliary disease such as autoimmune diseases, choledocholithiasis, viral hepatitis, systemic lupus erythematosus and cavernous hemangioma [10]. However, no paper to date has reported DJS associated NASH.

Most commonly, mild elevation of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) on routine blood work prompts the initial evaluation for NAFLD. In others, a finding of hepatic steatosis on an ultrasound performed for a different reason prompts the diagnostic workup. AST and ALT elevations are typically mild, ranging from 1–3 times the level of normal. In some cases, mildly high alkaline phosphatase and GGT can be observed. However, albumin, globulin, bilirubin and prothrombin time is within normal limits except for cirrhotic patients [11]. Liver biopsy provides the most accurate and specific data for the diagnosis and progression of NAFLD [3].

In conclusion, concomitance of bilirubin elevations to high serum transaminase levels and jaundice history since childhood in patients with non-cirrhotic steatohepatitis should be considered hereditary conjugated hyperbilirubinaemia such as DJS.

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