International Journal of Science and Research (IJSR)
ISSN: 2319-7064
SJIF (2020): 7.803

Direct Hyperbilirubinemia in Non-Obstructive Elderly Jaundice Patient - A Case Report

Diah Pradnya Paramita[1], Ketut Suryana[2]

[1]Department of Internal Medicine, Wangaya Regional Hospital, Denpasar, Bali, Indonesia

Correspondence: Diah Pradnya Paramita, Department of Internal Medicine, Wangaya Regional General Hospital, Bali, Indonesia
Email correspondence: *pradnyadiah[at]yahoo.com*

Abstract: ***Bilirubin is a product of the breakdown of haemoglobin. Bilirubin is taken up and goes conjugation process within the hepatocyte before transported out from liver to biliary tract. Dubin Johnson syndrome (DJS) is an inherited disorder caused by defect of ABCC2 gene which codes protein production that substantial to transport the conjugated bilirubin out from liver. It presented intermittent jaundice and usually come in young adult rarely in elderly. This rare disorder was not easy to diagnose, often misdiagnosed with extra hepatic obstruction. We present uncommon case of DJS with transaminitis that appears first in elderly. This is a case of previously unrecognized DJS precipitated by pulmonary infection in AIDS patient.***

Keywords: Dubin Johnson syndrome, direct hyperbilirubinemia, jaundice

1. Introduction

Bilirubin is resulted from the breakdown of hemoglobin and prematurely destroyed erythroid cells in the bone marrow. Bilirubin circulates in the blood bound to albumin and is taken up by hepatocytes in the liver. Within hepatocytes, bilirubin is conjugated with glucuronic acid then is secreted into bile [1]. Hyperbilirubinemiais a condition defined as elevated serum or plasma bilirubin levels above the reference range of the laboratory. It can be caused by conditions leading to predominantly indirect hyperbilirubinemia and those characterized by predominantly directhyperbilirubinemia. Directhyperbilirubinemia is usually secondary to hepatocellular disease or cholestasis (intrahepatic and extra-hepatic). Early workup and diagnosis is necessary for the appropriate management and to prevent future complications. Pathologic elevation of conjugated or direct bilirubin (concentration higher than 2 mg/dL or more than 20% of total bilirubin) is termed directhyperbilirubinemia. It is a biochemical marker of cholestasis and hepatocellular dysfunction. Following etiologies can affect any age group, but are more commonly observed in adult patients [2].

DJS is one of inherited disorders of bilirubin metabolisms. It is abenign genetic liver disorder, leading to accumulation of bilirubin, which is normally excreted by the liver into the bile [3].It is characterized by chronic or intermittent direct hyper-bilirubinemia, with chronic idiopathic jaundice as the main clinical manifestation [4]. DJS is caused by mutation of ATP binding cassette subfamily C member (ABCC2) gene that codes for a protein called multidrug resistance protein 2 (MRP2) productions. This protein moves substances out of the cell and is found mainly in the liver but is also present in the kidneys, the intestine, and the placenta. The normal functioning protein works to secrete bilirubin into the bile, which is then transported to the gallbladder where it is stored [3].

Incidence of DJS in the general population is unclear, it appears to be slightly more common in males and its incidence varies widely with ethnicity and geography. Most patients with DJS are often young adults and are asymptomatic. First recognition of the disease in old age is unusual. DJS is somehow found as an incidental finding while undergoing routine testing or being tested for some other unrelated problem. They may rarely present with mild icterus, weakness, and/or upper abdominal pain. Approximately 80% to 99% of people with DJS have intermittent jaundice caused by excess bilirubin (bile pigment) that cannot be excreted normally [5]. DJS is a rare and benign condition but it is not easy to diagnose and often misdiagnosed as biliary obstruction or hepatitis [3].

We present a case of DJS in elderly precipitated by current pulmonary infection in patient with AIDS admitted at Wangaya Regional Hospital Denpasar. The purpose of this case presentation is to remind medical professionals to consider possible congenital causes as a differential diagnosis in jaundiced patients with direct hyperbilirubinemia.

2. Case Report

A 66-year-old male patient was admitted to the Wangaya Regional Hospital with chief complaint of severe diarrhea without blood or mucous since 3 days before admitted. The patient also complained nausea causing hehad low appetite and low intake. Patient felt weakness all over the body since 7 days prior to hospital. The patient was conscious but appeared to be seriously ill. He admitted due to hypovolemic shock and hypoglycaemia. The patient was given fluid and glucose resuscitation in emergency room. During hospitalization patient showed icteric on sclera. History of diabetes mellitus, hypertension, dyslipidemia, or cardiovascular disease in patient and his family were denied. He has no smoking and alcohol habits previously.He diagnosed with AIDS, pulmonary tuberculosis, anemia and organic psychotic and was admitted two weeks ago. The patient is on second week of anti-tuberculosis therapy and had not started antiretroviral therapy yet.

On examination patient was conscious with blood pressure 120/80 mmHg after fluid resuscitation, respiratory rate 20 times per minute, temperature 36.6 degree Celsius, and heart rate 124 beats per minute. From physical examination there are, slight pale on conjunctivas, and oral thrush in cavumoris. Abdominal examination showed increased bowel sound, liver was not palpable, spleen was absent. From laboratory examination we found slight increase in leukocyte 10.20x10^3/µL (4.0-10.0), anemia10.9 g/dL (13.0-18.0), tranaminitis with alanine transaminase level (ALT): 84 U/L, : aspartate transaminase level (AST) 121 U/L (AST< 33, ALT< 50), increase blood urea nitrogen 54 mg/dL (10-50), and hyponatremia125 mmoL/L (130-145). Serological markers for hepatitis were negative. Chest x-ray revealed a pulmonary tuberculosis infection.

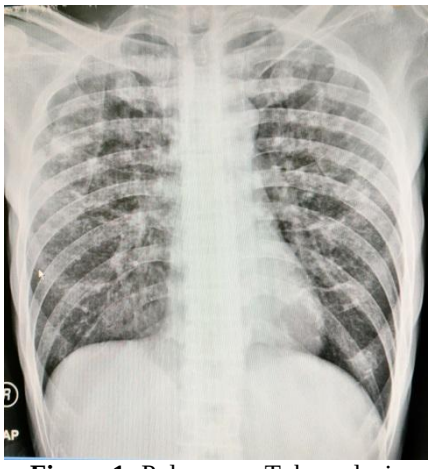

Figure 1: Pulmonary Tuberculosis

On the second day of hospitalization, patient still had diarrhea, with dark stool and blood on it, the urine was red due to anti tuberculosis drug. The patient started presented icteric sclera and complaint of slight abdominal pain in the right upper quadrant on palpation. Stigmata for chronic liver disease were not found. Fever and pruritus were denied. The patient has never had jaundice before. Historiesof liver disease, liver infection, and malignancy were denied. Laboratory examination revealed hyperbilirubinemia 8.73 mg/dL (<1.3) with direct bilirubin dominance 7.83 mg/dL (<0.5). This patient then undergoes more examination to find the cause of direct hyperbilirubinemia. Abdominal ultrasonography (USG) showed no cholelithiasis and cholecystitis, other organs were within normal limits. Protein analysis revealed normal alkaline phosphatase (ALP) 54 U/L (53-128), normal gamma glutamyltranspeptidase 52 U/L (<66), and low albumin level 2.5 g/dL (3.4-4.8). We exclude all the differential diagnosis of direct hyper-bilirubinemia and diagnosed this patient as DJS, hypovolemic shock related to acute diarrhea (improved), anemia, transaminitis, pulmonary tuberculosis on treatment, oral candidiasis, AIDS, and low intake.

The patient was started normal saline fluid combined with dextrose 10% infusion, cefoperazoneantibiotic intravenous every 12 hours, esomeprazole intravenous every 24 hours, tranexamic acid every 8 hours intravenously, nystatin drop per-oral every 8 hours, and activated attapulgite and pectin per-oral every 8 hours if diarrhea was still. No additional therapy was given to treat DJS. On the tenth day of hospitalization the patient's condition got worsened. The patient had decreased of consciousness, fever and massive bloody diarrhea. We had not performed colonoscopy to explore the cause of hematochezia because the patient's condition is unstable. The patient then died due to sepsis.

3. Discussion

This case ilustrated an elderly patient with AIDS who developed jaundice on the second day of hospitalization. Jaundice is said to be the first time it appears. Hyperbilirubinemia especially direct hyperbilirubiniemia can come from intrahepatic and extrahepatic problems. Extrahepatic etiologiesarecholelithiasis, pancreatitis (chronic and acute), and malignancies of pancreatic or biliary. Viral hepatitis, alcoholic hepatitis and non-alcoholic steatohepatitis, cirrhosis, drugs and toxins, also inherited disorders of bilirubin metabolisms come from intrahepatic problems [1]. Several supporting examinations such as laboratory and imaging tests are needed to make diagnosis [2].

ALP and gamma glutamyltranspeptidase levels are used to evaluate post hepatic obstruction. Gamma glutamyltranspeptidase may distinguish the hepatic source of increased ALP from alternate sources such as bone. A rise in these enzymes suggests the presence of cholestasis and may necessitate bile duct imaging. USG performed to exclude biliary obstruction, it also enables the assessment of parenchymal liver diseases, including cirrhosis, steatosis, congestion, and tumor. ALP and gamma glutamyltranspeptidase levels were within normal limits. This is supported by abdominal USG whichrevealed no obstruction in biliary tract and no inflammation or liver parenchymal abnormalities, the other organs are within normal limits. These two examinations then exclude the cause of direct hyperbilirubinemia from post hepatic obstruction.

Serologic studies for viral hepatitis conducted to identify potential etiologies. Hepatitis virus infection was ruled out since the serological markers were negative [2]. AST and ALT level are tested as markers of hepatocellular injury. ALT increases are more specific to liver injury. This patient had bilirubin level that is twice upper normal limit but the raised of ALT was less than three times upper limit of normal, so it did not meet the criteria of drug induced liver injury (Hy's law) [6]. We did not perform abdominal CT scan and liver biopsy due to facilities limitation.

We confirmed the diagnosis as DJS with transaminitis.The patient started normal saline fluid combined with dextrose infusion, antidiarrheal agent, cephalosporin third generation antibiotic, proton pump inhibitors, antifungal medication per-oral, and antifibrinolytics. No additional therapy was given to treat DJS. In this patient, DJS first appeared in old age, triggered by pulmonary infection.

DJS can present insidiously but is often precipitated by other diseases or by periods of major stress, including infection, pregnancy, hormonal and surgery. DJS usually common in younger age, some case present in elderly coinciding with another disease. A recent case reported DJS present

coincidence with colon cancer in elderly patient [7, 8].DJS should be considered when the common causes for direct hyperbilirubinaemia have been excluded, and patient has an increased percentage of direct bilirubin relative to total bilirubin concentration [9].

DJS is a benign disease, does not progress to fibrosis or development of cirrhosis, and does not require any treatment. Diagnosis of DJS can be made based on the presence of direct hyperbilirubinemia with no other abnormality of liver function tests, but the coincidence with another disease or pathologic stimulus can modify the clinical picture and results of laboratory tests, including histomorphology. However, liver biopsy is not a recommendation for making a diagnosis [9, 10].

4. Conclusion

DJS is a rare genetic disorder and is often misdiagnosed. DJS should be considered as a differential diagnosis when direct hyperbilirubinemia is present. This is important to avoid unnecessary therapy or procedure since DJS does not require any treatment. DJS may be unrecognized because it usually asymptomatic until it appears co-incident with another disease. Invasive medical procedures to establish the diagnosis of DJS are not always necessary.

5. Declarations

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: Not required

References

[1] Fargo M V., Grogan SP, Saguil A. Evaluation of jaundice in adults. *Am Fam Physician* 2017; 95: 164–168.
[2] Nishant T, Ishwarlal J. *Conjugated Hyperbilirubinemia*. StatPearls Publishing, https://www.ncbi.nlm.nih.gov/books/NBK562172/ (2020).
[3] Gensler R, Delp D. Dubin Johnson Syndrome. *National Organization for Rare Disorders*, https://rarediseases.org/rare-diseases/dubin-johnson-syndrome/ (2020, accessed 7 July 2021).
[4] Piccinelli M. Clinical cases. *Psicoter e Sci Um* 2020; 8960: 481–489.
[5] Dame N, Rabinowitz S. Dubin Johnson Syndrome, https://rarediseases.org/rare-diseases/dubin-johnson-syndrome/ (2020, accessed 5 July 2021).
[6] Devarbhavi H. An Update on Drug-induced Liver Injury. *J Clin Exp Hepatol* 2012; 2: 247–259.
[7] Kularatnam GAM, Dilanthi HW, Vidanapathirana DM, et al. Dubin-Johnson syndrome and intrahepatic cholestasis of pregnancy in a Sri Lankan family: A case report. *BMC Res Notes* 2017; 10: 1–5.
[8] LeVee A, Cooper C, Russell MB, et al. Dubin-Johnson Syndrome Presenting During Cardiac Transplantation Evaluation. *Cureus* 2020; 12: 8–12.
[9] Sticova E, Elleder M, Hulkova H, et al. Dubin-johnson syndrome coinciding with colon cancer and atherosclerosis. *World J Gastroenterol* 2013; 19: 946–950.
[10] Talaga Z, Vaidya P. *Dubin Johnson Syndrome*. StatPearls Publishing, https://www.ncbi.nlm.nih.gov/books/NBK536994/#_NBK536994_pubdet_ (2020).