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Case Report

Complex Sources of Hyperbilirubinemia

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Abstract

The authors present a case of a patient with severe hyperbilirubinemia due to acute hepatitis B infection which resolved without intervention with subsequent normalization of synthetic and excretory liver function. Despite this, the patient remained jaundiced due to unconjugated hyperbilirubinemia in the context of a recent diagnosis and flare of hereditary spherocytosis. Due to the complex clinical presentation, the patient underwent a liver biopsy with the additional genetic diagnosis of Gilbert's Syndrome being established. This illustrates an unusual case of both Hepatitis B and hereditary spherocytosis being a potential cause for a flare of Gilbert Syndrome.

Case Report

A 59-year-old Australian man returned from a 3-week holiday in Taiwan. On his return to Australia, he became progressively unwell with nausea, loss of appetite, and dark urine. During his holiday, he reported having unprotected sexual intercourse but denied heavy alcohol use, other illicit substance use, or other high-risk behaviours. He was otherwise well man with no other significant medical history and not on any regular medications. Social history revealed a non-smoker and social alcohol intake of two glasses of wine each evening. In regard to family history, the patient was adopted, and family history could not be traced.

He was up to date with vaccinations including Covid-19. On review at the General Practitioner (GP), he had normal vital signs but was markedly jaundiced with the yellow sclera. His abdomen was soft and non-distended with mild tenderness in the epigastrium and right upper quadrant. There was no organomegaly. The remainder of his examination was unremarkable.

His initial investigations included

Full Blood Count (FBC), Urea, Electrolytes, Liver function tests, ESR, CRP, serology and Polymerase chain reaction (PCR) for Hepatitis A, B, C, D, and E, serology for Chlamydia, Herpes simplex virus (HSV), Gonorrhoea, Human immunodeficiency virus (HIV), Syphilis, Trichomoniasis, Human papillomavirus (HPV), Epstein Barr Virus (EBV), Cytomegalovirus (CMV), Coxsackievirus and Toxoplasmosis, Thin and Thick blood film for Malaria, and Ultrasound for the abdomen in addition to Urine and Stool examination. Of the investigations mentioned above, abnormalities were detected in the following results-Liver function was grossly abnormal with Alanine aminotransferase (ALT) of 3000 IU/L (20-

45IU/L), Aspartate aminotransferase (AST) of 2000 IU/L (20-40 IU/L, Gamma glutamyltransferase 170 IU/L (10-30 IU/L), Bilirubin 400 umol/L(2-20umol/L) with 50 % conjugated bilirubin, Alkaline phosphatase 150 IU/L (2-17 IU/L), Albumin 30 g/L (40-60g/L). INR 1.1, PTT 40 seconds (30-40), D Dimer 0.3(<0.50), APTT 60 seconds (60-80).

Serology for hepatitis A showed positive IgG and negative IgM (either past infection or immunization), and serology for hepatitis C, D, and E were all negative for recent infection. However, hepatitis B serology was consistent with acute infection- Hepatitis B surface antigen (HBsAg) was positive, Hepatitis B e-antigen (HBeAg) was positive, Hepatitis B surface antibody (HBsAb) was negative, Anti-Hepatitis B core IgM (anti-HBc IgM) was positive, Anti-Hepatitis B core IgG (anti-HBc IgG) was negative, serum hepatitis B DNA was 2000 IU/ml. HIV serology and p24 antigen were negative, ultrasound for the liver was unremarkable, and COVID rapid test and PCR were negative.

Based on the above investigations, the patient was diagnosed with acute hepatitis B infection and advised to stay at home with close monitoring of liver function tests. The patient started to improve after two weeks with improvement in clinical and biochemical parameters. After 6 weeks, the patient seroconverted and tested positive for HBsAb and Hepatitis B e-Antibody (HBeAb), ALT, and AST started to normalize. Despite this, the patient remained jaundiced. Repeat bilirubin after two months was 450 umoles /L(20-40umoles/L), and repeated blood testings showed normal liver function, however, the Hemoglobulin dropped to 12g/dl (14-16g/dl) but all other blood testings including repeat viral hepatitis screen were either negative or inactive. The patient went on to have an autoimmune liver panel with the following investigations tested either negative or normal-Antinuclear antibody (ANA), Anti-dsDNA, Anti- Smith (Sm) antibody, Anti-soluble liver antigen, Anti-liver-kidney microsomal (LKM) antibody, anti-mitochondrial antibodies, Serum and urine copper, Serum ceruloplasmin, alpha one antitrypsin (AAT) protein, iron studies and genetic tests for hemochromatosis, carbohydrate-deficient transferrin, Thyroid function and Synacthen test.

Subsequently, the patient was referred to a hepatologist who proceeded with a liver biopsy. The histopathology was examined by two pathologists in two different hospitals, both pathologists agreed there were no structural abnormalities, apart from the increased agranular endoplasmic reticulum, and mild deposition of glycogen, in addition to increased lipofuscin pigment in the centrilobular region, these features had been reported before in Gilbert syndrome. The patient then went on to have genetic testing for Paroxysmal Nocturnal Haemoglobinuria (PNH) with flow cytometry, and for Gilbert and Crigler-Najjar

syndrome. UG1A1 *28 (uridine diphosphate-glucuronosyltransferase) mutation confirmed the diagnosis of Gilbert syndrome.

Blood film results received from a haematologist regarding the same patient confirmed a few spherocytes, a mild increase in reticulocytes, and a direct antiglobulin test was negative which ruled out autoimmune hemolytic anaemia. Additionally, the patient tested positive for eosin-5′-maleimide (EMA) binding by flow cytometry, and a repeat ultrasound of the abdomen did not show any gallstones or splenomegaly. Testing for cryoglobulin was negative, Glucose 6 phosphate dehydrogenase (G6PD) level was within normal range and Parvovirus IgM was negative. The patient was diagnosed with Gilbert syndrome and mild asymptomatic hereditary spherocytosis and was reassured and discharged back to his GP with advice that should he have any abdominal pain it could be due to pigmented gall stone.

Discussion

Jaundice is defined as the yellowish pigmentation of the skin, sclera, and mucosa due to hyperbilirubinemia. It is clinically detectable when the circulating bilirubin is greater than 35umol/L. Hyperbilirubinemia can be further classified as Conjugated (Direct) and Unconjugated (Indirect) hyperbilirubinemia. Unconjugated hyperbilirubinemia is due to increased production, impaired hepatic uptake, and decreased hepatic conjugation of bilirubin.

The common causes of Unconjugated Hyperbilirubinemia in adults are

A. Hemolytic Anemia: Immune-mediated (ABO incompatibilities, Auto-immune hemolytic anemia); non-Immune mediated (Sepsis, Microangiopathic hemolytic anemia, Liver disease); Extra-vascular causes (G6PD deficiency, Pyruvate Kinase Deficiency, Hereditary spherocytosis, PNH, Hemoglobinopathies, hypersplenism)

B. Congenital: Gilbert Syndrome and Criger Najjar syndrome

C. Drugs induced: Chloramphenicol, Gentamicin, pregnaneidol

Conjugated hyperbilirubinemia is caused by hepatic or cholestatic diseases. The common

causes of conjugated hyperbilirubinemia can be further classified into

1) Hepatocellular: Hepatitis, cirrhosis

2) Cholestatic causes- Primary biliary cirrhosis, Congenital (Dubin-Johnson syndrome. Rotor Syndrome); Drugs, Hepatitis, obstructive CBD pathologies.

Fractionation of total bilirubin and test for urinary bilirubin help to determine the type of hyperbilirubinemia. If conjugated bilirubin is less than 20% of the total- it is predominantly unconjugated and if it is more than 50% it is predominantly conjugated hyperbilirubinemia. Moreover, the presence of urinary bilirubin is consistent with conjugated hyperbilirubinemia [1-3]. Gilbert syndrome is the most common inherited cause of unconjugated hyperbilirubinemia. It is caused due to mutation in the promoter region of the UGT1A1 gene, which results in reduced UDP-glucuronosyltransferase (UGT) production [4,- 8]. The most common genotype of Gilbert syndrome is the homozygous polymorphism A(TA)7TAA in the

promoter of the gene for UDP-glucuronosyltransferase 1A1 (UGT1A1), which is a TA insertion into the promoter designated

UGT1A1*28. Patient usually has asymptomatic mild unconjugated hyperbilirubinemia usually triggered by fasting, haemolytic reactions, febrile illnesses, menstruation, physical exertion, infection, and dehydration [14]. Gilbert syndrome can coexist with hereditary spherocytosis and present with moderate unconjugated hyperbilirubinemia [15]. It has been found in patients who are hepatitis B carriers but not active hepatitis B. However, there are no case reports for acute Hepatitis B infection as a trigger for Gilbert syndrome so far.

In conclusion, Gilbert syndrome is a benign autosomal recessive liver disease characterized by unconjugated non-haemolytic hyperbilirubinemia due to defective glucuronidation of bilirubin secondary to a reduction in the activity of UGT with a good prognosis. Its management is conservative with observation and does not require any pharmacotherapy. The present case has shown the association of acute Hepatitis B infection as a trigger for Gilbert syndrome and highlights the importance of considering it as one of the differentials diagnoses for precipitating undiagnosed Gilbert syndrome. However, diagnosis of Gilbert syndrome requires careful clinical assessment and ruling out other common causes of unconjugated hyperbilirubinemia including haemolytic anaemia before proceeding with the genetic analysis of the UGT1A1 gene [9-13].

Acknowledgement

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Conflict of Interest

No conflict of interest.

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