CLINICAL VIGNETTE

Hyperbilirubinemia: Avoiding the Million Dollar Work Up

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Case Report

A 68-year-old man with a history of coronary artery disease status post drug eluting stent three years ago, hypertension, atrial fibrillation, and obstructive sleep apnea presents to clinic for routine check-up. His medication list includes aspirin, atorvastatin, carvedilol, and fish oil. On physical exam, he is a well appearing Asian-American man. His cardiac, pulmonary, abdominal and skin exam were normal. On review of his prior laboratory results, a complete blood count (CBC) was normal and a comprehensive metabolic panel (CMP) was notable for a bilirubin of 2.8; fractionation of bilirubin was not available. His remaining liver function tests, including alkaline phosphatase, albumin, aspartate transaminase and alanine transaminase were within normal range.

On further interview, the patient provides a history of jaundice years ago after eating shellfish, as well as being told he "might have hepatitis" after attempting to donate blood in the past. He denies any alcohol or illicit drug use. He is in a monogamous relationship with his wife and denies any other risky behaviors. Overall, the patient reports feeling well, with no changes in his oral intake or bowel movements. His stools are normal in color, consistency and regularity. The patient asks if he should be concerned about his elevated bilirubin.

Discussion

Hyperbilirubinemia is a common clinical problem, and although laboratories can vary in reference ranges, it is generally defined by a bilirubin level above 1.0 (normal 0.0 to 1.0 mg/dL). Jaundice, which is an abnormal yellow-to-orange discoloration of skin and mucous membranes produced by accumulation of bile pigment, may be difficult to detect on physical exam, especially in individuals with darker skin complexion, and may not be detected on exam until bilirubin levels are above 3.0.[1] For the clinician, identifying the etiology often poses a diagnostic challenge as the differential is broad and varies in significance. Generally, the variety of disorders include hepatic inflammation, bilirubin overproduction such as hemolytic anemia, impaired bilirubin conjugation, and biliary obstruction.

In order to avoid unnecessary and costly tests, it is useful to review normal and abnormal pathophysiology of bilirubin metabolism.

Normal Metabolism

Starting with a senescent red blood cell (RBC), which is phagocytosed with production of unconjugated bilirubin (UCB) in the final heme-degradation process. UCB is then bound by albumin and transported through the blood to be taken up by liver hepatocytes. The liver then conjugates the UCB into conjugated bilirubin (CB), which is now water soluble and secreted into the bile duct and into the intestinal tract. Intestinal bacteria convert CB to urobilinogen (UBG), which ultimately gives stool its brown color. UBG is reabsorbed, most of which returns to liver (90%) and kidneys (10%), which produces the yellow appearance of urine.[2]

To summarize: RBC breaks down into UCB → UCB bound by albumin is delivered to liver → UCB is conjugated to CB in the liver → CB secreted into bile duct and intestinal tract → CB then metabolized by intestinal bacteria to UBG → UBG reabsorbed to liver (90%) and kidneys (10%).

Bilirubin Overproduction

In bilirubin overproduction, extravascular hemolysis (e.g. hemolytic anemia) produces increased serum levels of UCB, which is metabolized by the liver into CB and proceeds through the normal process. As a result, there is an overall increase in bilirubin, which leads to darker stool and urine color. There is also a mild increase in serum aspartate transaminase (AST) as this is also contained within red blood cells. However, the remaining liver function tests, including alkaline phosphatase, albumin and alanine transaminase are unaffected. In summary, extravascular hemolysis leads to a predominantly unconjugated hyperbilirubinemia with mildly elevated AST. Also, one would expect some degree of anemia due to destruction of RBCs.

Impaired Liver Metabolism

In impaired liver metabolism (e.g. viral, drug, or alcoholic hepatitis), damage to hepatocytes impair the ability to conjugate UCB to CB. Consequently, UCB levels increase since the damaged hepatocytes cannot uptake the bilirubin, which leads to a mixed UCB and CB hyperbilirubinemia. This hepatic injury is also reflected in elevation in the other liver function tests (AST, ALT, and alkaline phosphatase). Urine bilirubin is also increased since UBG that normally is 90% reabsorbed to the liver is now shunted to the kidneys. In summary, impaired liver metabolism due to hepatitis leads to a mixed UCB and CB

hyperbilirubinemia, elevated AST, ALT and AP along with increased urinary bilirubin.

Besides viral hepatitis, impaired liver metabolism can also occur in hereditary conditions, such as Gilbert's syndrome, which is a common autosomal recessive or dominant defect affecting 5% of the population, males more than females. In contrast to viral hepatitis, there is no hepatic injury reflected in AST or ALT, but simply a reduced hepatic enzyme's ability to conjugate UCB to CB. In contrast to hepatitis, the urine bilirubin level is normal in Gilbert's syndrome.

Other types of hereditary impairments, such as Crigler-Najjar syndrome is incompatible with life. Physiologic jaundice and breast milk jaundice are seen in newborns.

Biliary Obstruction

In biliary obstruction (e.g. gallstone or malignancy), there is a block after UCB has already been conjugated in the liver. This obstruction prevents CB from entering the intestinal tract, which leads to back-flow pressure causing a serum increase in CB. In addition, since CB is no longer available in the intestinal tract, less is available to be converted by intestinal bacterial to UBG, which leads to pale colored stool and light-colored urine. There also be an increase in alkaline phosphatase due to obstruction of the bile duct. AST and ALT are mildly elevated due to the back-flow pressure damage to hepatocytes. In summary, biliary obstruction leads to CB hyperbilirubinemia, elevated AP, pale and pale stools and light-colored urine.

Besides biliary obstruction, disorders that decrease biliary outflow, such as primary biliary cirrhosis, Dubin-Johnson Syndrome, and Rotor's syndrome can cause similar conjugated hyperbilirubinemia.

Returning to our patient, we can now approach our patient's hyperbilirubinemia in a more stepwise manner. His bilirubin of 2.8 is certainly above the reference range of normal, and the next step would be to identify the bilirubin fractionation. We repeated liver function tests, which showed a predominantly unconjugated hyperbilirubinemia, and the remaining liver tests were again normal. At this point, the normal liver tests make both a viral hepatitis and biliary obstruction very unlikely. This is consistent with the history, as a viral hepatitis typically presents with gastrointestinal symptoms and obstruction with pale stool, neither of which were reported by the patient. Therefore, the patient's isolated unconjugated hyperbilirubinemia suggests either an overproduction of bilirubin (i.e. extravascular hemolysis) or a more benign process such as Gilbert's syndrome. Before ordering further tests, we suspect hemolysis seems less likely given the lack of anemia and normal serum AST level. Nonetheless, a urine analysis was checked and showed a normal Bilirubin level.

With an unconjugated hyperbilirubinemia and normal urine bilirubin, the patient was informed that he had a benign diagnosis of Gilbert's syndrome. Only two tests were required to confirm this test: liver function chemistries and urine analysis. No further testing or treatment was required.

Regarding his supposed history of hepatitis, we checked routine HCV and HBV serologies, and he was found to have native immunity to Hepatitis B. No further testing or treatment was indicated.

Conclusion

Hyperbilirubinemia is a common clinical problem that requires an understanding of the normal and abnormal metabolism of bilirubin. When faced with a hyperbilirubinemia, determining the bilirubin fractionation is key to guiding the next steps in diagnostic testing. Our patient was diagnosed with Gilbert's syndrome, which is a benign disorder and the most common cause of hereditary jaundice. It was diagnosed with two tests, a liver function test and urine analysis.

REFERENCES

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