JAMA Diagnostic Test Interpretation

Evaluating Elevated Bilirubin Levels in Asymptomatic Adults

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A 57-year-old white man presents for evaluation of an asymptomatic elevation in bilirubin detected on a chemistry panel during an annual physical examination. Thirty years ago, he had abnormal liver function tests attributed to use of an unknown medication that resolved when the drug was discontinued. He reports no jaundice, pruritus, or family history of liver disease and takes no medications. He drinks 1 alcoholic beverage daily (≈100 g/week). On physical examination, blood pressure was 108/63 mm Hg, pulse rate was 61 beats per minute, and body mass index (calculated as weight in kilograms divided by height in meters squared) was 23.4. His liver was 7.0 cm by percussion and nontender, sclera were anicteric, there was no stigmata of chronic liver disease, and splenomegaly was absent. The examination was otherwise unremarkable. His laboratory values are reported in the **Table**.

HOW DO YOU INTERPRET THESE TEST RESULTS?

A. Hyperbilirubinemia due to cholelithiasis

B. Hyperbilirubinemia due to Dubin-Johnson syndrome

C. Hyperbilirubinemia due to Gilbert syndrome

D. Hyperbilirubinemia due to hemolysis

Table. Simultaneously Obtained Serum Laboratory Tests

Laboratory Test	Patient's Value	Reference Range
Alanine aminotransferase, U/L	19	0-48
Aspartate aminotransferase, U/L	16	0-40
Alkaline phosphatase, U/L	66	30-115
Total bilirubin, mg/dL	2.5	0-1.0
Direct (conjugated) bilirubin, mg/dL	0.3	0-0.2
Indirect (unconjugated) bilirubin, mg/dL	2.2	0.2-0.7
Hemoglobin, g/dL	14.6	13.0-17.5
Platelet count, $\times 10^3/\mu L$	243	140-390
Haptoglobin, mg/dL	71	30-200
Lactate dehydrogenase, U/L	200	105-333

SI conversion factors: to convert U/L to μkat/L, multiply by 0.0167; mg/dL to μmol/L, multiply by 17.104.

Answer

C. Hyperbilirubinemia due to Gilbert syndrome

Test Characteristics

Bilirubin is the normal by-product of the breakdown of hemoglobin. 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, a process catalyzed by uridine diphosphoglucuronate-glucuronyltransferase (UDP-GT). Conjugated (direct) bilirubin is secreted into bile. This process is normally highly efficient so plasma unconjugated (indirect) bilirubin concentrations remain low. Hyperbilirubinemia can be caused by conditions leading to predominantly unconjugated hyperbilirubinemia and those characterized by predominantly conjugated hyperbilirubinemia (**Figure**). Diseases that increase the rate of bilirubin formation (eg, hemolysis, dyserythropoiesis), reduce hepatic uptake of bilirubin (eg, medications [gemfibrozil, irinotecan and the protease inhibitors, atazanavir, and indinavir]; portosystemic shunts), or reduce the rate of bilirubin conjugation (eg, Gilbert syndrome) result in increased levels of indirect bilirubin (Figure).

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Gilbert syndrome, also known as Gilbert-Meulengracht syndrome, is a hereditary condition with incomplete penetrance, characterized by intermittent unconjugated hyperbilirubinemia in the absence of hepatocellular disease or hemolysis.[1] Gilbert syndrome is present in 5% to 10% of Western European populations and patients are frequently unaware of their diagnosis.[2,3] A genetic variant in the promoter region of the *UGT1A1* gene, which encodes for UDP-GT, is associated with Gilbert syndrome and there is an additional thymine-adenine (TA) base pair in the TATA box instead of the normal 6 pairs.[2] In Gilbert syndrome, there is a 70% reduction in the liver's ability to conjugate bilirubin that can lead to intermittent episodes of nonpruritic jaundice, which are precipitated by fasting, infection, and overexertion.[3] Several therapeutic drugs including gemfibrozil, irinotecan, atazanavir, and indinavir inhibit UDP-GT activity and can trigger jaundice episodes in Gilbert syndrome.[4]

The diagnosis of Gilbert syndrome as the cause of hyperbilirubinemia should only be made after excluding other liver and hematologic disorders. Patients with Gilbert syndrome are asymptomatic and typically have otherwise normal liver serum chemistries. If the unconjugated bilirubin fraction predominates, hemolytic disorders and rare familial hyperbilirubinemias must be considered. In Gilbert syndrome, the degree of hyperbilirubinemia is typically less than 5 mg/dL and the conjugated bilirubin is typically less than 20% of the total bilirubin fraction.[3] The Medicare midpoint reimbursement for a total and direct serum bilirubin is $9.25 for each.[5] The cost of *UGT1A1* gene analysis ranges from $75 to $103, although it is rarely used for diagnosis.[6]

Application of Test Results to This Patient

Gilbert syndrome is the most likely cause of the unconjugated hyperbilirubinemia in the setting of normal liver enzymes and in the absence of medications that reduce hepatic uptake of bilirubin or

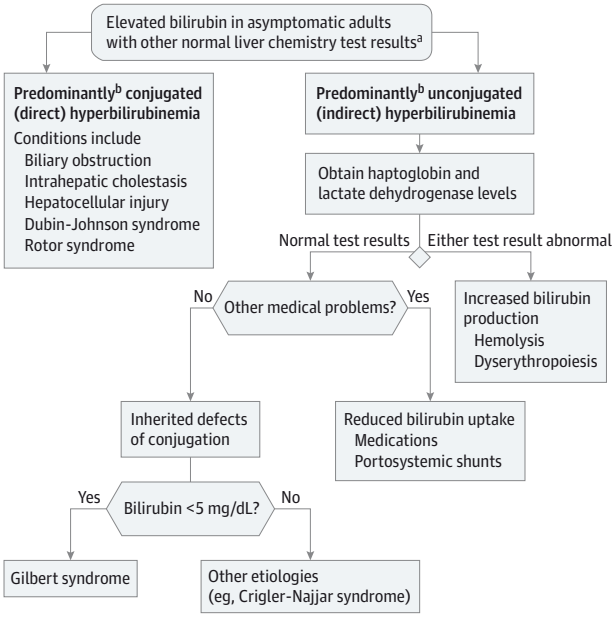

Figure. Suggested Diagnostic Approach to Hyperbilirubinemia Based on Clinical Experience

The algorithm has not been validated and is based on the authors' expertise and experience.[a]Includes alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase.[b]Indicates at least 80% of the total bilirubin fraction.

symptoms suggesting hepatobiliary disease or hemolysis. Dubin-Johnson syndrome is another benign hereditary condition characterized by a predominantly conjugated hyperbilirubinemia but would not explain the unconjugated hyperbilirubinemia.

Gilbert syndrome is typically diagnosed in the first 3 decades of life and no specific management is required for most patients. The Gilbert syndrome genotype is associated with an increased risk of gallstones[1,7] and adverse reactions to multiple drugs, including chemotherapy.[1,4,6,7] It is possible but unclear if elevated serum bilirubin levels protect against cardiovascular or other diseases.[8,9] A recent study reported an association of Gilbert syndrome with a 50% reduction in mortality compared with the general population (24 vs 50 deaths per 10 000 person-years).[10] Another study suggested that Gilbert syndrome may be associated with an increased risk for breast cancer.[1,4]

What Are Alternative Diagnostic Testing Approaches?

Hemolysis and drug-induced hyperbilirubinemia should be excluded. Presence of hemolysis can be evaluated with a peripheral blood smear and levels of lactate dehydrogenase and haptoglobin. Provocation tests, including observing an increase in unconjugated bilirubin after a 48-hour fast, are not recommended.[3] The diagnosis of Gilbert syndrome can be made in patients who continue to have normal laboratory results (other than the elevation in serum bilirubin) during the next 12 months. For cases in which diagnostic uncertainty remains, such as total bilirubin of greater than 5 mg/dL, genetic testing for a *UGT1A1* mutation can be performed although this is rarely necessary. Liver or biliary imaging and referral to a specialist are typically not needed. Overtesting may be deleterious to otherwise healthy patients with this benign condition.

Patient Outcome

In this patient, a peripheral blood smear, lactate dehydrogenase, and haptoglobin levels confirmed the absence of hemolysis. Repeat bilirubin measured 6 and 12 months later was elevated and a diagnosis of Gilbert syndrome was made. The patient remains well and follows up with his primary care physician for routine medical care.

Clinical Bottom Line

- Gilbert syndrome is a hereditary condition characterized by a 70% reduction in the ability to conjugate bilirubin, resulting in asymptomatic intermittent unconjugated hyperbilirubinemia.
- Gilbert syndrome is present in 5% to 10% of Western European populations.
- In Gilbert syndrome, the degree of hyperbilirubinemia is typically less than 5 mg/dL and the conjugated bilirubin is typically less than 20% of the total bilirubin fraction.[3]
- Gilbert syndrome is usually a diagnosis of exclusion and can be diagnosed by ruling out intrinsic hepatic disease and hemolytic states.

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