Unconjugated Hyperbilirubinemia

Key Points:
- Gilbert’s Syndrome is an inherited defect in the UDP-glucuronosyltransferase enzyme resulting in unconjugated hyperbilirubinemia (levels near 3 mg/dL).
- Diagnosis is clinical: elevated indirect bili, normal CBC/smear/retics, and normal LFT’s.
- Crigler-Najjer Types I and II are rare inherited defects in the same enzyme resulting in markedly elevated indirect bilis and potentially kernicterus (type I).

Definition/Basics
- Three mechanisms can explain elevated unconjugated hyperbilirubinemia:
  1. Overproduction of bilirubin (hemolysis, hematoma, dyserythropoiesis).
  2. Reduced bilirubin uptake (CHF, cirrhosis, and Gilbert’s Syndrome).
  3. Impaired bilirubin conjugation (Gilbert’s, Crigler-Najjar, others).

Gilbert’s Syndrome

Pathogenesis
- Inherited disorder of bilirubin glucuronidation.
- Mutation in the promoter region of the UGT1A gene which causes decreased UGT production.
- UGT = Uridinediphosphoglucuronate glucuronosyltransferase.
- 9% of population in Western world is homozygous, 30% heterozygous.

Clinical Features
- Isolated elevated unconjugated (indirect) hyperbilirubinemia.
- Levels typically less than 3 mg/dL.
  - Can increase to as high as 6mg/dL in hemolysis, fasting, febrile illness, stress, physical exertion and after nicotinic acid (?).
  - Steroids can decrease levels.
- May be more susceptible to toxic effects of drugs that require glucuronidation.
  - Tylenol, tolbutamide, irinotecan.

Diagnosis
- Presumptive clinical diagnosis is patients have the following:
  - Unconjugated hyperbilirubinemia on repeated testing.
  - Normal CBC, blood smear, reticulocyte count.
  - Normal liver function tests.

Crigler-Najjer Syndromes (Type I and II)

Pathogenesis
- Mutations in the UGT1A1 gene, resulting in absent (type I) or markedly reduced (type II) UDP-glucuronosyltransferase activity; incredibly rare.

Clinical Features
- Elevated serum bilirubin: 20-50 mg/dL in type I, < 20mg/dL in type II.
- Type I associated with kernicterus (acute and chronic bilirubin encephalopathy).

Diagnosis
- Clinical diagnosis similar to Gilbert’s.

Treatment
- Phototherapy, plasmapheresis, or liver transplant for Type I.
- No treatment for type II but can give phenobarb (decreases bili 25%).