Crigler-Najjar Syndrome Type 1

Crigler-Najjar syndrome, type I is an inherited disorder of bilirubin metabolism that occurs when there is complete absence of UDP-glucuronosyltransferase, an enzyme responsible for forming insoluble bilirubin into a conjugated, water-soluble form. Without this enzyme, unconjugated bilirubin rapidly accumulates in infants who will die within the first two years of life if left untreated.

PLAY PICMONIC

Pathophysiology

Autosomal Recessive
Recessive-chocolate
This is an extremely rare disease that is inherited in an autosomal recessive pattern.

Absent UDP-glucuronosyltransferase
Missing Upside Down Pineapple cake with Glue-transformer
This enzyme is responsible for processing unconjugated, lipid-soluble bilirubin into conjugated, water-soluble bilirubin that can be excreted. Unlike Gilbert’s disease in which a patient still retains some enzymatic function, there is total lack of this enzyme in Crigler-Najjar type I so unconjugated bilirubin quickly rises to toxic levels.

Symptoms

Neonatal Jaundice
Newborn Jaundice-janitor
Due to highly elevated bilirubin at birth and the inability to excrete it, neonates will have persistent jaundice within a few days of life.

Kernicterus
Colonel
Because excess unconjugated bilirubin is lipid-soluble, it can cross the blood-brain-barrier (BBB) and deposit in the gray matter, causing permanent CNS damage. Kernicterus results in poor growth and development and is the most common cause of death in Crigler-Najjar type I.

Diagnosis

Normal Liver Function Tests
Normal Liver with Test-tubes
Liver enzymes such as AST and ALT are not typically affected in this disease.

Elevated Unconjugated Bilirubin
Up-arrow Un-conga Belly-ribbon-dancer
Bilirubin levels are usually in the range of 20-25 mg/dL, but may reach up to 50 mg/dL in Crigler-Najjar type I. Both Crigler-Najjar type I and Gilbert’s syndrome show elevated levels of unconjugated bilirubin, which serves to contrast them from Dubin-Johnson or Rotor syndrome that involve increased conjugated bilirubin levels. Stool color will be normal.

Treatment

Phototherapy

Photo-flash

When neonatal skin is exposed to certain wavelengths of fluorescent light, it accelerates the conversion process of unconjugated bilirubin into an excretable form. The jaundiced infant is exposed to phototherapy lamps for up to 12 hrs/day.

Plasmapheresis

Plasma-fairy

Similar to dialysis in which whole blood is removed from the body, filtered and cleaned by a machine, and returned to the patient, plasmapheresis filters plasma only and can rapidly remove undesirable substances bound to albumin, such as unconjugated bilirubin.

Calcium Phosphate and Orlistat

Calcium-cow with Phosphate-P and Oar-with-fat

Calcium phosphate is given orally and works by binding bilirubin in the GI tract to prevent reabsorption and assist excretion; it is best used in conjunction with phototherapy. Orlistat is a lipase inhibitor that decreases absorption of fats in the GI tract; since unconjugated bilirubin is lipid-soluble, less fat absorption means less bilirubin absorption and increased excretion.

Death often by Age 2

Death at (2) Tutu birthday cake

Unless a patient is rapidly diagnosed and treated with the above mentioned therapies, these patients will die before the age of two due to the irreversible CNS effects of kernicterus. The only definitive long-term treatment is liver transplant.

Considerations

No Response to Phenobarbital

Liver Not Responding to Phantom-Barbara-doll

Crigler-Najjar syndrome, type II, also called Arias syndrome, is distinct from type I because these patients still retain some functioning UDP-glucuronosyltransferase enzymes. The two types can be distinguished by administering phenobarbital, a barbiturate and P450 inducer that increases liver enzyme synthesis. With type II, unconjugated bilirubin levels will decrease as the remaining enzymes are increased after administration of phenobarbital. Unconjugated bilirubin levels remain elevated in type I disease, due to complete absence of the enzyme, as phenobarbital cannot increase the enzyme levels if they are not being made.