Review Article

Epidemiology and Management of Unconjugated Hyperbilirubinemia

Abstract:

Unconjugated hyperbilirubinemia is characterised by increased serum or plasma bilirubin (unconjugated) levels that exceed the laboratory's reference range. Unconjugated hyperbilirubinemia, is the most common cause of jaundice in newborns. Unconjugated hyperbilirubinemia is caused by bilirubin metabolism dysregulation, which includes increased synthesis, reduced hepatic absorption, and decreased bilirubin conjugation. Gilbert syndrome, Crigler-Najjar syndromes type I and II, and hereditary illnesses producing hemolytic anaemia are all examples of inherited conditions that can cause unconjugated hyperbilirubinemia. Crigler-Najjar syndrome is a highly rare condition, Gilbert syndrome is more common yet less dangerous symptom. Using phototherapy and plasmapheresis, the major goal of treatment is to lower the amount of unconjugated bilirubin. Intensive phototherapy is the basis of treatment for Crigler-Najjar type I syndrome. Combined with plasmapheresis and in some cases liver transplantation may be required.

Introduction:

Unconjugated hyperbilirubinemia is characterised by increased serum or plasma bilirubin (unconjugated) levels that exceed the laboratory's reference range. Unconjugated hyperbilirubinemia is caused by bilirubin metabolism dysregulation, which includes increased synthesis, reduced hepatic absorption, and decreased bilirubin conjugation. Unconjugated hyperbilirubinemia is prevalent in infants, and high bilirubin (UCB) levels can lead to life-threatening kernicterus. [1] Increased synthesis, poor conjugation, or reduced hepatic absorption of bilirubin, a yellow bile pigment generated after erythrocyte breakdown, can all lead to unconjugated hyperbilirubinemia. It can also happen to babies in their natural state. Crigler-Najjar syndrome type 1, a kind of unconjugated hyperbilirubinemia, kills most children before they reach adulthood if they are not treated effectively. [2]

Unconjugated hyperbilirubinemia, is the most common cause of jaundice in newborns. A bilirubin-induced encephalopathy or kernicterus occurs in infants when the elevated concentration of UCB crosses the blood-brain barrier and deposits in the basal ganglia or cerebellum. Gilbert syndrome, Crigler-Najjar syndromes type I and II, and hereditary illnesses producing hemolytic anaemia are all examples of inherited conditions that can cause unconjugated hyperbilirubinemia. [1,3-5]

Crigler-Najjar syndrome is a rare autosomal recessive hereditary illness in which UDP-glucuronosyltransferase, an enzyme essential for the glucuronidation of unconjugated bilirubin in the liver, is absent or has diminished activity. It is one of the most common causes of non-hemolytic congenital jaundice. The sole cause of illness manifestation is a rise in the levels of unconjugated bilirubin. The severity of the condition is determined by the quantity of enzymes created during the glucuronidation of bilirubin. Based on clinical criteria such as molecular and functional characteristics, severity of clinical presentation, and phenobarbitol response, Crigler-Najjar syndrome is divided into two categories. Type I is the most severe, with nearly total lack of UDP-glucuronosyltransferase enzyme activity, and type II is milder, with decreased enzyme activity. [6]

Etiology & Pathophysiology:

The catabolic result of heme metabolism is bilirubin, a yellow-orange bile pigment. About 85% of the heme moiety originates from red blood cell haemoglobin degradation, with the rest coming from inefficient erythropoiesis and the breakdown of other hemoproteins such cytochromes, myoglobin, and catalase. The reticuloendothelial system's microsomal heme oxy-genase enzyme transforms heme to biliverdin, which is then reduced to unconjugated bilirubin (UCB) by a second enzyme called biliverdin reductase. The UCB is a lipophilic bacteria. The liver transports UCB firmly linked to albumin. The mechanism of UCB entrance into the liver is unknown, although the best candidate appears to be a bilirubin transporter. UCB dissociates from albumin in liver hepatocytes and attaches to glutathione-S-transferases family proteins, which present it for conjugation and prevent it from leaving the liver. The enzyme UDP-glucuronosyltransferase (UGT1A1) then conjugates unconjugated bilirubin with

one or two molecules of glucuronic acid, resulting in bilirubin monoglucuronide and bilirubin diglucuronide, respectively. [1,7,8]

Free (unbound) bilirubin is taken up by liver hepatocytes and transformed to conjugated bilirubin, but unconjugated bilirubin is lipid soluble and travels easily through cell membranes to bind to albumin in blood. Conjugated bilirubin is a water-soluble pigment that is carried from liver hepatocytes to the biliary tract system, where it is eliminated in the stool. Some conjugated bilirubin is reabsorbed in the intestines before being eliminated as urobilinogen by the kidneys. When this metabolic process is disrupted, it results in a rise in unconjugated bilirubin (e.g., from increased red blood cell death or impaired bilirubin conjugation) or conjugated bilirubin (e.g., from increased red blood cell destruction or impaired bilirubin conjugation) (e.g., from hepatocellular damage or biliary tract obstructions). [9]

The rate at which freshly produced bilirubin enters the plasma (bilirubin turnover) and the pace at which irreversible bilirubin is removed by the liver define the plasma concentration of unconjugated bilirubin (hepatic bilirubin clearance). The precise classification of cases of unconjugated hyperbilirubinemia into those caused by increased bilirubin turnover (for example, hemolysis), those caused by decreased bilirubin clearance (for example, Gilbert's syndrome), and those caused by both mechanisms is possible using kinetic studies with radiolabeled bilirubin. [10]

Because of a genetic deficiency in the bilirubin-uridine diphosphate glucuronosyltransferase (UGT1A1) gene, Crigler-Najjar syndrome is caused by a lack of or decreased amount of the enzyme UDP-glucuronosyltransferase. A loss, variations in intron splice donor and receptor sites, missense mutations, exon skipping, insertion, or the development of a stop codon within the UGT1A1 gene result in total deficiency of the enzyme UDP-glucuronosyltransferase in type I Crigler-Najjar syndrome. Type II Crigler-Najjar syndrome, on the other hand, is caused by a point mutation in the UGT1A1 gene, which leads in reduced synthesis of the enzyme UDP-glucuronosyltransferase. [6,11-13]

Epidemiology:

When serum bilirubin levels are about 5mg/dL, around 50% of full-term and 80% of preterm newborns develop jaundice in the first 2 to 4 days after delivery.

Crigler-Najjar syndrome is a highly rare condition, with less than fifty instances reported in the United States and about one case per million births globally. Gilbert syndrome is more common in the United States, with around 9% of the population homozygous for the UGT1A1 mutation. Gilbert syndrome is caused by mutations in the UGT1A1 gene that are distinctive to ethnic groups. Gilbert syndrome, for example, is frequently linked to a mutation in the TATAA element of the UGT1A1 promoter region in white people. Male newborns are more likely to have neonatal jaundice, although Crigler-Najjar syndrome is not gender-related. Gilbert syndrome is more frequent in males than females throughout puberty, which may be attributed to males' higher rate of bilirubin production. Breast milk jaundice develops in 0.5 to 2.4 percent of newborns between days 2 and 5 after delivery owing to increased enterohepatic bilirubin circulation. [1,14,15]

Signs and symptoms:

- ineffective erythropoiesis (production of early labelled bilirubin [ELB]) Is characterised by asymptomatic jaundice.
- Type 1 Crigler-Najjar syndrome - Jaundice appears in the first few days of birth and increases fast by the second week; patients may show signs of kernicterus, which includes hypotonia, deafness, oculomotor palsy, lethargy, and, eventually, death.
- Crigler-Najjar syndrome type 2 - This disease entity is characterised by the absence of clinical signs except for the presence of jaundice.
- Gilbert syndrome - On clinical examination, it may simply appear as jaundice; at least 30% of Gilbert syndrome patients are asymptomatic, while nonspecific symptoms such as stomach cramps, weariness, and malaise are prevalent.
- Physiologic neonatal jaundice is clinically evident in 50% of newborns within their first five days of life.
- Nonphysiologic neonatal jaundice - Maternal serum jaundice, also known as Lucey-Driscoll syndrome, is an autosomal recessive metabolic disorder that affects the enzymes involved in bilirubin metabolism. It causes a transient familial neonatal unconjugated hyperbilirubinemia, with jaundice occurring within the first four days of life. [2]

Evaluation:

The history and physical examination are used to assess jaundice. Fractionated bilirubin, a complete blood count, alanine transaminase, aspartate transaminase, alkaline phosphatase, -glutamyltransferase, prothrombin time and/or international normalised ratio, albumin, and protein should all be included in the first laboratory examination. Extrahepatic obstructive and intrahepatic parenchymal diseases can be distinguished using ultrasound or computed tomography imaging. Ultrasonography is the least intrusive and cost-effective way of imaging. Additional cancer screening, biliary imaging, autoimmune antibody testing, and a liver biopsy may all be part of a more thorough examination. [9]

The findings of liver testing in Crigler-Najjar syndrome type 1 are normal except for elevated blood unconjugated bilirubin levels. Bilirubin levels in the blood vary from 20 to 50 mg/dL. Serum is devoid of conjugated bilirubin, while urine is devoid of bilirubin. A high-performance liquid chromatography of bile or a tissue enzyme assay of a liver biopsy sample are required for a definitive diagnosis of Crigler-Najjar syndrome. [2]

Laboratory: Fractionated bilirubin, a complete blood count, alanine transaminase, aspartate transaminase, -glutamyltransferase, alkaline phosphatase, prothrombin time and/or international normalised ratio, albumin, and protein should all be tested in the laboratory to discover the cause of jaundice. To distinguish between conjugated and unconjugated hyperbilirubinemia, fractionated bilirubinemia is necessary. A complete blood count along with a peripheral blood smear can assist detect hemolysis and rule out chronic illness anaemia and thrombocytopenia, both of which are frequent in decompensated cirrhosis. Hepatocellular injury might be indicated by elevated alanine transaminase and aspartate transaminase levels. In chronic liver illness, however, levels may be normal (e.g., cirrhosis). There may not be enough normal liver parenchymal tissue to produce high quantities of these enzymes in such circumstances. [9]

Gilbert's syndrome can be detected even when there is simultaneous hemolysis because to the ability to measure hepatic bilirubin clearance. Gilbert's syndrome is the most frequent yet harmless of the inherited bilirubin metabolism diseases, whereas Crigler-Najjar syndrome is uncommon but deadly. [10]

The genetic analysis detects the forms of mutations in the gene encoding the UGT1A1 enzyme in DNA collected from peripheral blood leukocytes, buccal scraping, and other tissues. Genetic analysis of chorionic villus samples or amniotic cells aspirated in amniotic fluid can be used to provide a prenatal diagnosis. In Crigler-Najjar type I syndrome, diffusion tensor imaging of the brain may aid in the detection of microstructural grey and white matter abnormalities. In established cases of hepatosplenomegaly, a liver biopsy and histopathologic examination can be used to assess liver cirrhosis. [6]

Imaging: Ultrasonography, computed tomography, and magnetic resonance cholangiopancreatography are noninvasive imaging techniques used in people with jaundice. Ultrasonography or computed tomography is the most common first-line method for evaluating blockage, cirrhosis, and vascular patency, with ultrasonography being the least restrictive and cost-effective technique. Magnetic resonance cholangiopancreatography or endoscopic retrograde cholangiopancreatography can be used to further examine the intra- and extrahepatic biliary tree, with the latter allowing for treatment options such as biliary stent implantation to ease blockage. Endoscopic ultrasonography, in conjunction with endoscopic retrograde cholangiopancreatography, can be used to assess common bile duct blockages and identify whether the obstruction is caused by a mass or a stone. [9,16-18]

Management:

Using phototherapy and plasmapheresis, the major goal of treatment is to lower the amount of unconjugated bilirubin. The majority of individuals survive adolescence without substantial brain injury, although they eventually develop kernicterus later in life. Currently, liver transplantation is the only treatment option for Crigler-Najjar type I syndrome. **Intensive phototherapy** is the basis of treatment for **Crigler-Najjar type I syndrome**. The treatment of newborn hyperbilirubinemia frequently includes phototherapy. Intensive phototherapy is more effective than traditional phototherapy because it produces a faster and more effective reaction. Intensive phototherapy also decreases late problems and reduces the length of treatment. Due to thicker skin, higher skin pigmentation, and a lower body surface area to body mass ratio, phototherapy is less effective in older children and adults. [6,19-21]

Gilbert syndrome patients do not require any special therapy because they are typically asymptomatic. To minimise superfluous testing in the patient and family members, it is more vital to recognise the illness and address the mechanism of inheritance. Phenobarbital can be used to reduce bilirubin levels in individuals with co-existing illnesses and elevated bilirubin levels by producing UGTs. [22]

Long-term phototherapy should be used in conjunction with plasma exchange to aid in the conversion of bilirubin to more soluble isoforms that can be eliminated in the urine. In Crigler-Najjar syndrome type 1, oral calcium phosphate may be a beneficial adjunct to phototherapy. (It should be noted, however, that phototherapy restricts the child's and his or her family's activities.) Phototherapy also causes insensible water loss, diarrhoea, skin tanning, and issues with body temperature regulation.) [2]

To avoid major neurological repercussions, when unconjugated bilirubin levels approach hazardous levels, the condition is treated with intensive intravenous fluid hydration, albumin therapy, and perhaps plasma exchange. Albumin infusion enhances the plasma-binding capacity of bilirubin, retaining bilirubin excess and lowers the total body exchangeable unconjugated bilirubin percentage, limiting its transport and storage in extravascular locations. Its usage is widely acknowledged in therapeutic settings. Ursodeoxycholic acid, lipid-rich meals, and calcium carbonate may be provided to improve intestinal flow or trap bilirubin in the intestinal lumen, increasing bilirubin and derivatives excretion with the faeces. However, such therapies have substantial limits and may come with considerable risks and unwanted side effects in some circumstances. [23-27]

Calcium phosphate supplementation: Patients with Crigler-Najjar type I who received phototherapy and calcium phosphate supplementation had an 18% drop in blood bilirubin, suggesting that calcium phosphate captures photoproducts of bilirubin discharged in the bile. This concept is also supported by animal experiments with rats, which found lower blood bilirubin levels following oral calcium phosphate supplementation, most likely due to unconjugated bilirubin being trapped in the gut. [6]

Allogeneic hepatocytes or hepatocyte progenitor cells transplantation therapies have the potential to heal hereditary liver diseases. In Crigler-Najjar patients, isolated allogenic hepatocyte transplantation has been attempted, but results

have been limited and temporary. After 9–11 months, the transplanted cells' engraftment was poor, and they had no growth advantage, resulting in a reduction in cell function, necessitating liver replacement. A recent cell transplantation experiment using mesenchymal stem cells had similar outcomes. To boost engraftment rate in animal models, many methods have been explored, including partial hepatectomy, irradiation, CCl4 therapy, and blocking endogenous hepatocyte growth. These therapies, however, cannot be used on patients, and safer alternatives must be discovered. [23,28-32]

Conclusion:

Unconjugated hyperbilirubinemia is without doubt one of the concerning conditions for modern medicine, as it's the most common cause of jaundice in newborns. Gilbert syndrome, Crigler-Najjar syndromes type I and II, and hereditary illnesses producing hemolytic anaemia are all examples of inherited conditions that can cause unconjugated hyperbilirubinemia. Crigler-Najjar is the least common yet the most dangerous and life-threating condition. Management of such condition depends on phototherapy and plasmapheresis and in some conditions liver transplantations. Currently there's trial for Allogeneic hepatocytes or hepatocyte progenitor cells transplantation therapies which have the potential to heal hereditary liver diseases. We hope for more research to help improve such treatments.

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