



Epidemiology and Management of Unconjugated Hyperbilirubinemia

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This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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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 (type 1 and 2), Crigler-Najjar syndromes (type 1 and 2), and hereditary illnesses producing hemolytic anaemia are all examples of inherited conditions that can cause unconjugated hyperbilirubinemia. Crigler-Najjar syndrome is a sporadic 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 management of Crigler-Najjar syndrome type 1. Combined with plasmapheresis and in some cases liver transplantation may be required.

Keywords: Unconjugated; hyperbilirubinemia; epidemiology; crigler-najjar syndromes.

1. 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. When a high concentration of UCB crosses the blood-brain barrier and deposits in the basal ganglia or cerebellum, it causes bilirubin-induced encephalopathy or kernicterus in infants. Gilbert syndrome, Crigler-Najjar syndromes type 1 and type 2, 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 genetic disorder in which UDP-glucuronosyltransferase, an enzyme required for the glucuronidation of unconjugated bilirubin in the liver, is either absent or has a reduced activity. It is one of the most common

causes of congenital non-hemolytic 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 features, clinical severity, and phenobarbital response, Crigler-Najjar syndrome is divided into two categories. Type I is the most severe, resulting in a near complete lack of UDP-glucuronosyltransferase enzyme activity, whereas type II is milder, resulting in reduced enzyme activity [6].

2. ETIOLOGY AND PATHOPHYSIOLOGY

The catabolic result of heme metabolism is bilirubin, a yellow-orange bile stain. Approximately 85% of the heme moiety is obtained from red blood cell haemoglobin degradation, with the remainder originating from inefficient erythropoiesis and the breakdown of many other hemoproteins like cytochromes, myoglobin, and catalase. The reticuloendothelial system's microsomal heme oxygenase enzyme transforms heme to biliverdin, which is then reduced to unconjugated bilirubin (UCB) by biliverdin reductase. The UCB bacteria is a lipophilic bacteria. UCB is transported by the liver and is tightly linked to albumin. The mechanism by which UCB enters the liver is unknown, but a bilirubin transporter appears to be the best candidate. UCB dissociates from albumin in liver hepatocytes and attaches to glutathione-S-transferase family proteins, presenting it for conjugation and preventing it from exiting 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].

Crigler-Najjar syndrome is caused by a genetic deficiency in the bilirubin-uridine diphosphate glucuronosyltransferase (UGT1A1) gene, which results in a lack or decreased amount of the enzyme UDP-glucuronosyltransferase. In type 1 Crigler-Najjar syndrome, 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. A point mutation in the UGT1A1 gene, on the other hand, causes reduced synthesis of the enzyme UDP-glucuronosyltransferase, resulting in type 2 Crigler-Najjar syndrome [6,11-13].

3. RISK FACTORS

These factors may cause doctors to test bilirubin levels shortly after birth: ABO incompatibility.

This occurs when a mother's blood type is O and her infant's blood type is A or B. Maternal antibodies to group A or B blood are transferred to the foetus and can cause hemolysis (the destruction of red blood cells) in the infant, resulting in hyperbilirubinemia.

Heavy bruising from delivery. Old blood can gather under the skin as a result of bruises, leading to an increase in bilirubin production.

Family history of any disorders that lead to increased hemolysis, like glucose-6-phosphate dehydrogenase deficiency.

- Infants born before the 35th week of pregnancy.
- A sibling who required treatment for hyperbilirubinemia at birth.
- East Asian race, as identified by the infant's parents.
- Jaundice noted within the first 24 hours of life.
- Massive weight loss, which could indicate that the infant isn't getting enough breast milk or formula [14].

4. EPIDEMIOLOGY

Once serum bilirubin levels are about 5mg/dL, approximately 50% of full-term and 80% of preterm newborns develop jaundice within the first 2 to 4 days after delivery. Crigler-Najjar syndrome is a very rare genetic condition, with fewer than fifty cases reported in the United States and about one case per million births worldwide. Gilbert syndrome is more common in the United States, where approximately 9% of the cohort is homozygous for the UGT1A1 mutagenesis. Gilbert disease is defined by ethnically specific mutations in the UGT1A1 gene. In white folks, Gilbert syndrome, for example, is frequently linked to a mutation in the TATAA element of the UGT1A1 promoter region. Although Crigler-Najjar syndrome is not gender-specific, male newborns are more likely to have neonatal jaundice. Throughout puberty, males are more likely than females to develop Gilbert syndrome, which may be due to males' higher rate of bilirubin production. Because of increased enterohepatic bilirubin circulation, breast milk jaundice develops in 0.5 to 2.4 percent of newborns between days 2 and 5 after delivery [1,15,16].

5. 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, commonly known as Lucey-Driscoll syndrome, is an autosomal recessive metabolic condition that affects bilirubin metabolism enzymes. It causes temporary familial unconjugated hyperbilirubinemia in newborns, with jaundice appearing within the first four days of life [2].

6. 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].

7. 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 gene sequencing detects gene mutations encoding the UGT1A1 enzyme in DNA extracted 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 performed to detect liver cirrhosis [6].

8. DIFFERENTIAL DIAGNOSIS

Unconjugated hyperbilirubinemia could be induced by bilirubin metabolism dysregulation,

which includes bilirubin production, hepatocyte uptake, and conjugation. Unconjugated hyperbilirubinemia should be distinguished from other diseases with comparable manifestations. Unconjugated bilirubin levels rise dramatically in hemolytic anemias and hematoma resorption. Hemolytic anemias can cause a slight increase in bilirubin levels, whether or not there are clinical symptoms. Hemolytic disorders such as glucose-6-phosphate dehydrogenase (G6PD) deficiency, sickle cell anaemia, thalassemia, and autoimmune disorders should be considered during the diagnostic process [17].

Genetic diseases of the enzyme glucuronosyltransferase (UGT1A1), such as Gilbert syndrome and Crigler-Najjar syndromes (CNS1 and CNS2), can obstruct complete bilirubin conjugation, resulting in varying degrees of unconjugated hyperbilirubinemia depending on the degree of enzyme inhibition with each disease. Other disorders that might cause defective bilirubin conjugation include portosystemic shunts, congestive heart failure, liver injury, dyserythropoiesis, and hyperthyroidism, and should all be evaluated during the diagnosis. Other factors to consider in the diagnosis of unconjugated hyperbilirubinemia include drug side effects (rifampicin, probenecid,

or other antibiotics), chronic liver diseases, thyrotoxicosis, infections, and physiologic neonatal jaundice caused by the immature conjugating ability of the UGT1A1 enzyme [18-20].

9. 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 [9,21-23] Fig. 1 and Fig. 2.

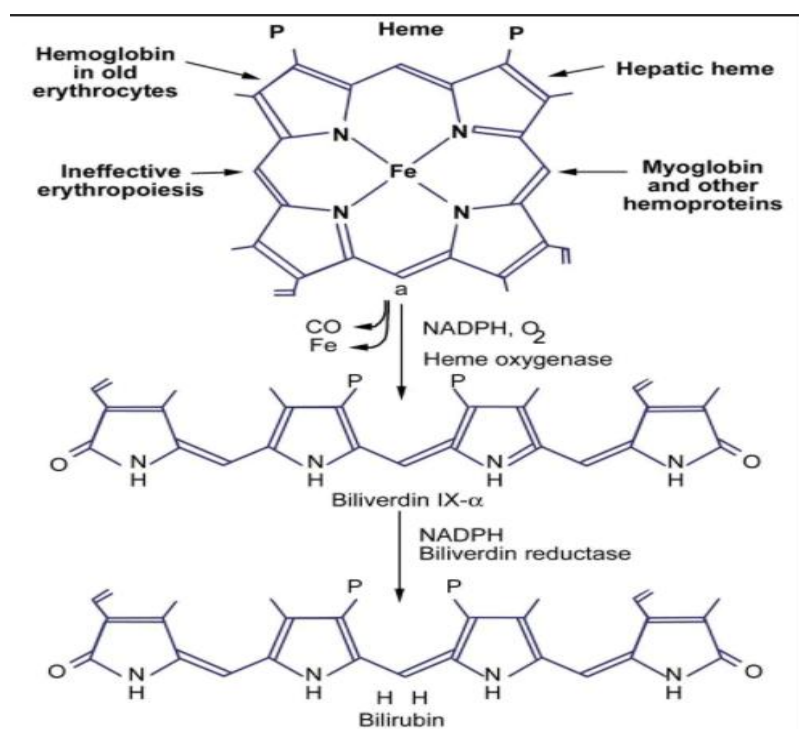


Fig. 1. Structure of Hemoglobin in erythrocytes

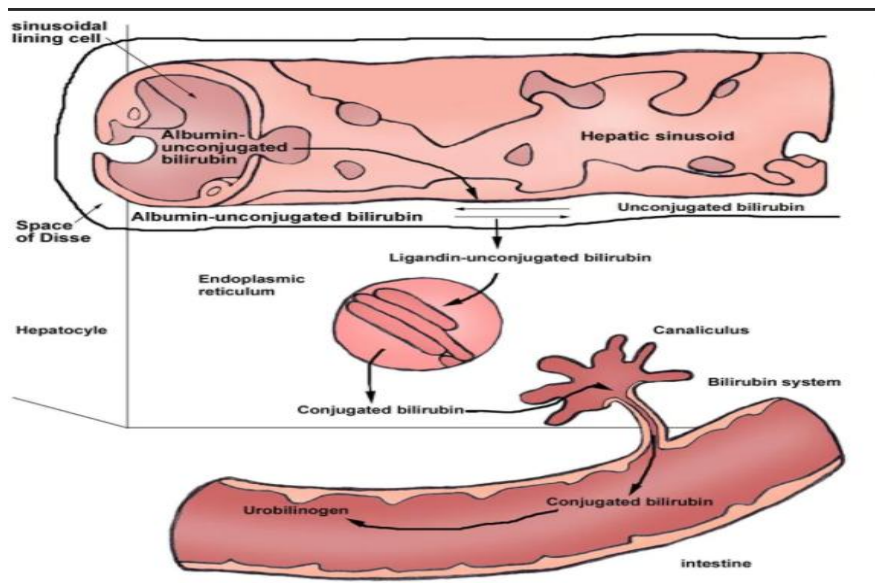


Fig. 2. Endoplasmic reticulum

10. 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 finally progress kernicterus future in life. Currently, the only treatment option for Crigler-Najjar type I syndrome is liver transplantation. The treatment for Crigler-Najjar type I syndrome is based on intensive phototherapy. Phototherapy is frequently used to treat newborn hyperbilirubinemia. Because it produces a faster and more effective reaction, intensive phototherapy is more effective than traditional phototherapy. Intensive phototherapy also reduces late complications and treatment duration. Phototherapy is less effective in older children and adults due to thicker skin, higher skin pigmentation, and a lower body surface area to body mass ratio [6,24-26].

Gilbert syndrome patients do not require any special therapy because they are typically asymptomatic. To minimize superfluous testing in the patient and family members, it is more vital to recognize 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 [27].

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 [28-32].

Calcium phosphate supplementation: Patients with Crigler-Najjar type 1 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 intestine [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 [28,33-38].

11. 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 1 and 2, 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-threatening 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.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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