# Crigler najjar syndrome: A systematic outline

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## Abstract
Crigler-Najjar Syndrome (CNS) is a rare genetic condition characterized by non-hemolytic unconjugated hyperbilirubinemia. It is caused by mutations in the UGT1A1 gene which codes for the enzyme uridine diphosphate glucoronosyl transferase-1, required for the conjugation and further elimination of bilirubin from the body. Affected individuals are usually asymptomatic apart from the jaundice and investigations reveal isolated indirect hyperbilirubinemia. It can be conveniently diagnosed by evaluating the response to phenobarbital in terms of decrease in bilirubin levels. Genetic testing of the UGT1A1 gene for mutations is the investigative clincher. The hallmark outcome of Crigler-Najjar syndrome is a determined yellowing of the skin, mucous membranes and the sclera of eye. There are two patterns of this disorder: Crigler-Najjar syndrome type I, characterized by a nearly complete lack of enzyme activity and severe symptoms; and Crigler-Najjar syndrome type II, characterized by inadequate enzyme activity and milder symptoms. Both forms are inherited as autosomal recessive characters and are caused by faults or mutations of the UGT1A1 gene. Treatment is engaged toward dropping the level of unconjugated bilirubin in the blood. Early treatment is vibrant in Crigler-Najjar syndrome type I to prevent the development of encephalopathy during the first few months of life. Because Crigler-Najjar syndrome type II is milder and responds to phenobarbital, treatment is different. The purpose of the current review article is to emphasize on causes, types, clinical symptoms, autosomal pattern, complications, management and future direction for treatment of Crigler-Najjar syndrome.

**Keywords:** Hyperbilirubinemia, Phenobarbitone, UGT1A1 gene, Bilirubin, Jaundice, Mutations.

## Introduction
Crigler-Najjar syndrome (CNS), named for the two physicians who first termed the disorder in 1952, John Crigler and Victor Najjar, is a life-threatening inherited ailment that affects the liver. CNS is a rare autosomal recessive disorder of bilirubin metabolism caused by complete or incomplete deficiency of hepatic microsomal bilirubin uridine 5'-diphosphate-glucuronosyl transferase (UDPGT) activity.[1] It is characterized by inborn unconjugated hyperbilirubinemia in the absence of liver disease as well as hemolysis.[2,3] Crigler-Najjar syndrome is likely to affect fewer than 1 in 1 million neonates worldwide. Many researchers believe that the disorder often goes undiagnosed or misdiagnosed making it difficult to determine its true incidence in the general inhabitants. It is likely more common than projected.[4,5]

Bilirubin is formed when erythrocytes are broken down. This ingredient is removed from the body only after it undergoes a chemical reaction in the liver, which converts the toxic form of bilirubin (called unconjugated bilirubin) to a less toxic form called conjugated bilirubin. Individuals with Crigler-Najjar syndrome have a backlog of unconjugated bilirubin in their blood (unconjugated hyperbilirubinemia). After the breakdown of hemoglobin from erythrocytes, it reduces to the heme molecule and protein complex. Heme molecule is also catalyzed and altered into biliverdin, which itself is ultimately converted to bilirubin by biliverdin reductase.[6] The bilirubin is unconjugated and water insoluble and therefore cannot be excreted in the urine and bile, but it is lipid-soluble and therefore crosses the blood-brain barrier as well as the placenta. Unconjugated bilirubin bonds to two glucuronic acid molecules in the liver by a UDP-glucuronyl transferase enzyme and transforms to conjugated bilirubin. Conjugated bilirubin is water-soluble and passes into bile and ejected into the small intestine.[7]

Bilirubin has an orange-yellow color, and hyperbilirubinemia causes yellowing of the skin and sclera of the eyes (jaundice). In Crigler-Najjar syndrome, jaundice is obvious at birth or in infancy. Severe unconjugated hyperbilirubinemia can lead to a condition called encephalopathy (kernicterus), which is a form of brain impairment caused by the accumulation of unconjugated bilirubin in the brain. Newborn with kernicterus are often tremendously exhausted (sluggish) and may have hypotonia.[8] These neonates may experience episodes of increased muscle tone (hypertonia) and bending of their backs. Kernicterus can lead to other neural problems, including involuntary twisting movements of the body, deafness, or cerebral disability. Crigler-Najjar syndrome is divided into two types. Type-1 is very severe, and affected individuals can die in childhood due to kernicterus, although with right treatment, they may stay alive longer. Type 2 is less severe. People with CNS-2 are less likely to develop kernicterus, and most exaggerated people survive into adulthood.[9,10]

### Causes
Crigler-Najjar syndrome caused by mutations in the UGT1A1 gene. This gene delivers instructions for making the bilirubin uridine diphosphate glucuronosyl transferase (bilirubin-UGT) enzyme, which is secreted chiefly in liver cells and is needed for the elimination of bilirubin from the body. The bilirubin-UGT enzyme carry out a chemical reaction termed as glucuronidation.[11] Throughout this reaction, the enzyme transfers glucuronic acid to unconjugated bilirubin, converting it to conjugated bilirubin. Glucuronidation forms bilirubin soluble in water so that it

can be removed from the body. Alterations in the UGT1A1 gene that cause Crigler-Najjar syndrome result in reduced or lacking function of the bilirubin-UGT enzyme. Individuals with CNS1 have no enzyme activity, while Individuals with CNS2 have less than 20 percent of normal function. The loss of bilirubin-UGT function declines glucuronidation of unconjugated bilirubin. This toxic material then accumulated in the blood, causing unconjugated hyperbilirubinemia and jaundice.[12] The serum bilirubin ranges from 3-20 mg/dL.[13]

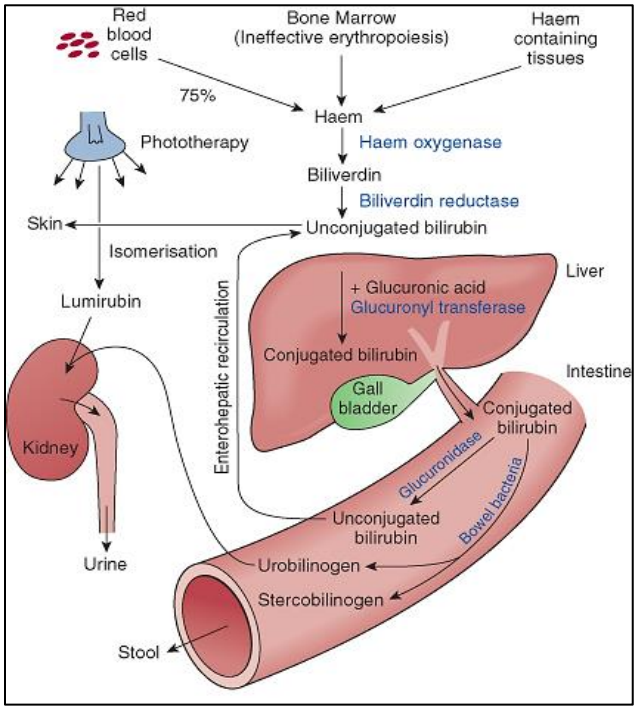


**Fig. 1:** Bilirubin metabolism and mechanism of phototherapy

**Inheritance pattern**

Crigler-Najjar syndrome is congenital in an autosomal recessive pattern, which means both copies of the UGT1A1 gene in each cell have mutations. This leads to in born fault of bilirubin metabolism due to complete deficiency of UDP-GT in CNS-1, and partial deficiency of UDP-GT in CNS-2. The affected infants have unconjugated hyperbilirubinemia from birth.[14] A less severe condition termed Gilbert syndrome can occur if one copy of the UGT1A1 gene has a mutation. It normally presents in juvenile age group especially in females due to rise in bilirubin production under the effect of stress (steroid) hormones.[15]

**Types of CNS**

Type 1 (CNS-1) is very severe, and affected people can expire in childhood due to encephalopathy. People with CNS-1 have enzyme function not at all. The lack of bilirubin-UDPGT activity declines glucuronidation of unconjugated bilirubin. This toxic substance then accumulates in the body, triggering unconjugated hyperbilirubinemia and jaundice.[16] Although with correct treatment, they may survive longer. Approximately 170 cases of CNS have been informed in the literature so far, almost 3 out of 76 cases were CNS-1. Crigler-Najjar Syndrome type I is less common than CNS-2 with serum bilirubin levels of untreated patients in left-over of 350 µmol/L. Crigler-Najjar Syndrome does not cause structural impairment to the liver but causes severe and life-threatening extra-hepatic impediments, mostly neurological. Encephalopathy is a serious complication of both CNS type 1 and type 2 and pronounces the staining of the basal ganglia such as globus pallidus and subthalamic nuclei and cranial nerve nuclei. In the most serious form, bilirubin encephalopathy leads to central deafness, oculomotor palsy, ataxic choreoathetosis, mental retardation, seizures, spasticity, and death. There are less severe forms, which lead to ataxia, deafness and slurred speech. A sudden deterioration of speech, handwriting and posture may develop during periods of high serum bilirubin levels.[17,18]

CNS-2 is less severe. Individuals with CNS-2 have less than 20 percent of normal function and less likely to develop kernicterus, and most affected individuals survive into adulthood. It is caused by mutations in the UGT1A1 gene which codes for the enzyme uridine diphosphate glucoronosyl transferase-1, required for the conjugation and further excretion of bilirubin from the body. Greater than 25% fall in bilirubin levels after treatment with phenobarbital distinguishes it from Crigler-Najjar type 1.[19,20]

**Indications of CNS**

The symptoms of CNS type I usually become seeming soon after birth. Affected new born baby develop severe jaundice, a yellowing of the skin, mucous membranes and sclera of the eyes. These symptoms endure after the first three weeks of life.[21]

Infants are at risk for developing bilirubin encephalopathy, well-known as kernicterus, within the first month of life. Kernicterus is a possibly serious neurological condition in which extreme levels of bilirubin accumulate in the brain, initiating injury to the central nervous system. Initial signs of bilirubin encephalopathy may comprise weakness (fatigue), nausea, illness, and/or disappointing feelings. Other symptoms include lack of certain reflexes; slight to severe muscle spasms, including spasms in which the head and heels are bent or arched backward and the body bows forward; and unrestrained skeletal muscle spasticity. In addition, affected infants may imbibe weakly; develop a high-pitched shout, and/or reveal weakened muscle tone, causing atypical "floppiness."[22]

Bilirubin encephalopathy can consequence in minor symptoms such as clumsiness, trouble with fine motor skills and underdevelopment of the enamel of teeth, or it can result in severe impediments such as hearing loss, complications with sensory perception, seizures, and slow, unceasing, uncontrolled, struggling movements of the arms and legs or the whole body. An episode of bilirubin encephalopathy can ultimately result in serious brain damage. Although bilirubin encephalopathy generally progresses early during infancy, in some cases, people with CNS type 1 may not develop bilirubin encephalopathy until

later in infantile or in early adulthood. Individual in which the blood bilirubin level is retained at safe levels by phototherapy can develop bilirubin encephalopathy at any age if the phototherapy is interrupted or the Individual is suffered by other illnesses.[23]

Crigler-Najjar syndrome type 2 is less severe than type 1. Some people have not been spotted until they are adults. Affected infants develop jaundice, which rises during times while a newborn is sickening, has persistent fasting. Kernicterus is sporadic in Crigler-Najjar syndrome type II, but can occur especially when an affected individual is sickening, fasting or under anesthesia.[24]

**Diagnosis**

A diagnosis may be suspected within the first few days of life in babies with persistent jaundice. A diagnosis may be confirmed by a systematic clinical assessment, distinctive findings, complete patient history, and specialized testing. For example, in infants with this disorder, blood tests state abnormally high levels of unconjugated bilirubin in the absence of hemolysis. In addition, bile analysis reveals no detectable bilirubin glucuronides and urine analysis may demonstrate absence of bilirubin. Genetic testing confirms finding of Crigler-Najjar syndrome. Genetic testing can spot mutations in the UGT1A1 gene that are recognized to cause the disorder.[25]

It is essential to differentiate Crigler-Najjar syndrome type I and type II. The administration of phenobarbital lessens blood bilirubin levels individuals exaggerated with Crigler-Najjar syndrome type II and Gilbert syndrome, but is ineffectual for those with Crigler-Najjar syndrome type I. Therefore, failure to respond to this medicine is a significant indication for differential diagnostic purposes.[26]

**Management of CNS**

The prime goal line of treatment for Crigler-Najjar syndrome is to decrease the amount of unconjugated bilirubin in the blood as promptly and steadily as possible. Treatment is performed by different methods for CNS type I and type II.[27]

CNS type I is primarily managed by phototherapy, in which the child is exposed to blue LED light in an apparatus similar to a tanning bed. During this procedure, the bare skin is exposed to intense light, while the eyes are shielded. The light bypasses the need for conjugation, and breaks down the unconjugated bilirubin, which can then be excreted into the bile and intestines for elimination. However, phototherapy is a tedious process, requiring 10-12 hours of therapy per day. The prolonged exposure to light causes the child's skin to thicken, increasing the need for a more intense phototherapy regimen. Exposure of skin to sun light is very effective in reducing blood bilirubin levels.[28]

Plasmapherersis has been used to rapidly lower bilirubin levels in the blood. Plasmapheresis is a method for eliminating unwanted substances including toxins, metabolic waste and plasma components from the blood. During plasmapheresis, blood is removed from the affected individual and blood cells are separated from plasma. The plasma is then replaced with other human plasma and the blood is transfused back into the affected patient.[29]

Liver transplantation is the only definitive treatment for individuals with Crigler-Najjar syndrome type-1. Liver transplantation has drawbacks such as cost, limited availability of a donor, need for prolonged use of immunosuppressive drugs and the potential of rejection. Some physicians recommend a liver transplant if infants or children with severely elevated levels of unconjugated bilirubin do not respond to other therapy (refractory hyperbilirubinemia) or if there is a progression of neurological symptoms. Other physicians believe that liver transplantation should be performed before adolescence as preventive therapy, before brain damage can result from early onset kernicterus. A new liver has the enzyme with the ability to convert unconjugated bilirubin (that is unable to be excreted from the body) into conjugated bilirubin (that is able to be excreted from the body). Patients still have the gene mutation causing the deficiency of glucuronyl transferase and can still pass the abnormality to their children.[30,31]

Crigler-Najjar syndrome type II responds to treatment with phenobarbital. In some instances, during an episode of severe hyperbilirubinemia, individuals with Crigler-Najjar syndrome type II may need phototherapy. Some affected individuals may not require any treatment, but should be monitored routinely.[32]

**Future direction for treatment of CNS**

Exploration on congenital errors of metabolism such as Crigler-Najjar syndrome is ongoing. Researchers are studying the origins of these disorders and attempting to design enzyme replacement therapies (ERT) that may return missing and/or deficient enzymes to the body. ERT has been successful in treating other metabolic disorders and research is underway to develop an ERT for Crigler-Najjar syndrome.[33]

Gene transfer therapy is also being considered as another approach to treatment for people with Crigler-Najjar syndrome. In gene therapy, the defective gene present in a patient is substituted with a normal gene to enable the production of the active enzyme and prevent the development and progress of the disease. Gene transfer therapy could be eternal, leading to life-long remedy of the disease. However, at this time, some technical problems need to be resolved before this type of gene therapy can be advocated. Other types of gene transfer that can reduce the bilirubin levels for several years, but not life time, is being considered for the treatment of Crigler-Najjar syndrome type 1. Researchers are studying whether the transplantation of liver cells (hepatocytes) are beneficial as a treatment of Crigler-Najjar syndrome. Because the liver is structurally sound in patients with Crigler-Najjar syndrome, investigators are exploring the possibility that transplanting hepatocytes may provide limited correction of the UGT1A1 enzyme deficiency. More studies are needed to determine the long-lasting effectiveness of this treatment. Like liver transplantation, hepatocytes transplantation also requires prolonged treatment with immunosuppressive medications.[34,35]

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None.

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