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## **Crigler-Najjar Syndrome - current state of knowledge, overview of etiology, symptoms, diagnosis and treatment methods**

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## **ABSTRACT**

Crigler-Najjar syndrome is an autosomal recessive genetic disorder characterized by a mutation in the UGT1A1 gene, resulting in a complete deficiency of uridine diphosphate glucuronosyltransferase enzyme in hepatocytes. This leads to jaundice due to elevated levels of indirect bilirubin in the blood. Two types of the syndrome are distinguished: type I and type II. Untreated disease can lead to serious complications, often necessitating liver transplantation. Therefore, there is a constant need for new treatment methods. This article provides an overview of the clinical symptoms, pathophysiological mechanisms, and current diagnostic and treatment methods for this condition. Although Crigler-Najjar syndrome is rare, its diagnosis and treatment pose clinical challenges due to potential complications associated with bilirubin accumulation. The article also discusses therapeutic perspectives, such as phototherapy and plasma exchange, and provides recommendations for patient care. Given the limited availability of information on Crigler-Najjar syndrome, this review aims to increase clinical awareness and improve the quality of care for patients with this rare disorder.

### **Aim of the study**

The aim of the review is to provide a comprehensive understanding of the clinical symptoms, pathophysiological mechanisms, and current diagnostic and treatment methods for this rare genetic disorder. The article seeks to increase clinical awareness among specialists from various medical fields and improve the quality of care for patients with Crigler-Najjar syndrome, considering potential complications and challenges associated with managing the disease.

### **Material and methods**

The article presents the current state of knowledge based on a review of scientific literature on Crigler-Najjar syndrome. Publications describing its etiology and pathogenesis, clinical picture, natural course, diagnostic methods, and treatment were reviewed. The review was conducted using the Google Scholar and PubMed platforms. The search included the keywords ‘Crigler-Najjar syndrome’, ‘liver transplantation’, ‘phototherapy’, ‘bilirubin abnormalities’, ‘liver diseases’, ‘UGT1A1 mutation’.

**Keywords:** Crigler-Najjar syndrome; liver transplantation; phototherapy; bilirubin abnormalities; liver diseases; UGT1A1 mutation

## **Introduction**

Crigler-Najjar Syndrome is a rare, genetically determined disease that causes severe neonatal jaundice. In this disease, there is an elevation of indirect bilirubin. If undiagnosed and untreated, it can lead to severe complications, including mental impairment and death. This publication aims to inform and sensitize the reader to this problem.

## **Etiology**

Crigler-Najjar syndrome is a genetic disorder caused by a mutation in the bilirubin-uridine diphosphate glucuronosyltransferase (UGT1A1) gene. This results in the absence or reduced levels of the enzyme UDP-glucuronosyltransferase. The disease can occur in two forms: type I and type II. [1, 2] In type I Crigler-Najjar syndrome, mutations may include deletions, changes in intron splice donor and acceptor sites, missense mutations, exon skipping, insertions, or the formation of stop codons within the UGT1A1 gene. All these changes lead to a complete deficiency of the enzyme UDP-glucuronosyltransferase. In contrast, type II Crigler-Najjar syndrome is caused by a point mutation in the UGT1A1 gene, resulting in reduced production of this enzyme. [3, 4, 5]

## **Epidemiology**

Medical data indicates that Crigler-Najjar syndrome is a rare disease. It is estimated to occur with a frequency of 0.6 to 1 per million live-born newborns worldwide. [6]

## **Types**

Type 1 was first described in 1952 by Crigler and Najjar. It is inherited in an autosomal recessive manner. The cause is a mutation in the UGT1A1 gene, resulting in a complete lack of the UGT enzyme in hepatocytes. Patients with Crigler-Najjar syndrome type 1 have total serum bilirubin levels exceeding 20 mg/dl (340  $\mu\text{mol/l}$ ) and can increase up to 50 mg/dl (850  $\mu\text{mol/l}$ ). This is the most severe form of the disease since patients completely lack enzyme activity. [7, 8] In these patients, bile is almost entirely composed of unconjugated bilirubin, with only trace amounts of monoglucuronide bilirubin. Symptoms appear within the first few days after birth and rapidly progress. Untreated patients are at risk of developing severe neurological disorders, including kernicterus, mental retardation, and in extreme cases, death.

In type 2, total serum bilirubin levels range from 3.5 to 20 mg/dl (60-340  $\mu\text{mol/l}$ ). The course of the disease is milder. It is inherited in an autosomal recessive manner. In these patients, UGT1A1 enzymatic activity is preserved at approximately 4%. This is sufficient to keep unconjugated bilirubin levels below the threshold for severe neurological damage. UGT1A1 enzyme levels can be increased through treatment with phenobarbital, which stimulates UGT1A1 gene transcription. [9, 10, 11]

## **Symptoms**

This disease manifests as rapidly increasing jaundice within the first few days after birth. Type 2 may also present later in life, between the ages of 2 and 10. Unconjugated bilirubin is transported throughout the body by the bloodstream with the help of albumin. Normally, the amount of unconjugated bilirubin is minimal, less than 0.2%. The symptoms are caused by the deposition of unconjugated bilirubin in various organs and lipophilic tissues, particularly in the brain.

During a physical examination, jaundice is visible, indicated by yellowing of the skin and sclera. The color of the stool is normal. Apart from jaundice, other test results are normal in both types of the syndrome, with no signs of liver disease. Older children may have scratch marks on their skin due to itching. In some cases, progressive liver dysfunction and various overlapping toxicities cause hepatosplenomegaly. In mild forms, neurological damage includes bilirubin-induced neurological dysfunction, which manifests as hypotonia, lethargy, and lack of appetite. Acute bilirubin encephalopathy initially presents with sleepiness, mild to

moderate hypotonia, and a high-pitched cry. In more severe cases, patients develop movement disorders such as abnormal gait, imbalance, difficulties in precise movements, and ataxia due to the deposition of bilirubin in the basal ganglia and cerebellum. The most severe stage is kernicterus, which involves the deposition of bilirubin in the brain, occurring mainly in the basal ganglia, globus pallidus, hippocampus, subthalamic nucleus, Ammon's horn, cranial nerve nuclei, and cerebellum. [12, 13, 14] Due to the toxic effects of bilirubin on the basal ganglia and brainstem nuclei responsible for oculomotor and auditory functions, patients may develop cerebral palsy, abnormal eye movements, hearing loss, and enamel hypoplasia. Lack of treatment at this stage inevitably leads to the patient's death. The advanced stage may present with seizures, apnea, and a semi-comatose or comatose state. Death may result from respiratory failure or seizures. [15] Elevated levels of unconjugated bilirubin can lead to the formation of gallstones. This process takes time, so it typically manifests later in life. Liver cirrhosis also develops gradually over a longer period. Most children born with Crigler-Najjar syndrome initially have a healthy liver. The mechanism leading to liver cirrhosis is not fully understood, but it may be caused by chronic bile stasis associated with gallstones, toxicity from drugs primarily metabolized in the liver, toxicity resulting from phototherapy, and hem degradation products. [16, 17]

## **Diagnosis**

The diagnosis of the disease requires a properly conducted clinical examination, considering the symptoms mentioned earlier, and confirmation through genetic testing. The performance of specialized molecular tests is conducted in specialized laboratories. An important aspect is differentiating between type I and type II, as they require distinct therapeutic approaches. In type I, high serum bilirubin levels are noticeable, which in newborns can exceed 40 mg/dl, with a lack of direct bilirubin in bile and no elevation of liver enzyme parameters. ALT, AST, and GGT are usually within normal limits. In type II, the serum bilirubin level is typically below 20 mg/dl. In this variant, the activity of other liver enzymes also remains within the normal range.

## **Treatment methods**

Treatment of Crigler-Najjar syndrome is a crucial factor influencing the reduction of complications and severe disorders in patients in the future. The main goal of treatment is to lower the level of unconjugated bilirubin using phototherapy and plasmapheresis. Most

patients survive into puberty without significant brain damage, but eventually develop kernicterus later in life. The only currently available curative option for Crigler-Najjar type I syndrome is liver transplantation. Treatment focuses on two main aspects. On one hand, it is important to control bilirubin and its neurotoxic effects (phototherapy, plasmapheresis, pharmacological treatment), and on the other hand, to restore UGT1A1 activity in hepatocytes (cell therapy and gene therapy). [18, 19, 20]

### **Phototherapy**

It is the primary form of treatment for Crigler-Najjar type I syndrome. Phototherapy is often used in the treatment of neonatal hyperbilirubinemia. Intensive light therapy is more effective than conventional therapy because it leads to a faster and more efficient response from the body. Additionally, it shortens the duration of treatment and reduces the risk of later complications. However, in older children and adults, phototherapy may be less effective due to thicker skin, increased pigmentation, and a lower ratio of body surface area to body mass. [18, 20]

### **Plasmapheresis**

Plasmapheresis is the most effective process for removing excess unconjugated bilirubin from the blood during hyperbilirubinemia crisis. Treatment with this method involves removing unwanted compounds and substances from the blood. During plasmapheresis, blood is extracted from the patient, and blood cells are separated from the plasma. The plasma is then replaced with donor plasma, and the blood is transfused back into the patient. Since bilirubin tightly binds to albumin, the removal of albumin during this process leads to a reduction in bilirubin levels in the blood.

### **Pharmacological Treatment**

This treatment includes drugs that increase enzyme activity (phenobarbital), bilirubin-binding agents (calcium phosphate, orlistat), cholagogues (ursodeoxycholic acid), and heme oxygenase inhibitors (tin-protoporphyrin, zinc-protoporphyrin). When unconjugated bilirubin reaches toxic levels, the disease is managed with aggressive intravenous fluid hydration, administration of albumin, and possibly plasma exchange to avoid serious neurological consequences. Albumin infusion increases the bilirubin plasma-binding capacity, capturing

excess bilirubin and thereby reducing the total exchangeable unconjugated bilirubin fraction in the body, preventing its movement and accumulation in extravascular sites. [21, 22, 23, 24] Its use is accepted in many clinical centers. Ursodeoxycholic acid, lipid-rich food, and calcium carbonate may be administered to increase intestinal flow or to trap bilirubin in the intestinal lumen, maximizing the elimination of unconjugated bilirubin and its derivatives in the feces. Orlistat is a lipase inhibitor that captures unconjugated intestinal bilirubin and aids in its excretion in proportion to the amount of fat excreted in the stool. [25, 26, 27]

### **Liver Transplantation**

Liver transplantation is the only therapeutic and definitive treatment method in Crigler-Najjar type I syndrome. The transplanted liver contains a healthy UGT1A1 enzyme for bilirubin conjugation, rapidly reducing serum bilirubin levels. Prophylactic liver transplantation is recommended to prevent kernicterus, as it may be irreversible once it occurs. Two main types of liver transplantation are used in the treatment of patients with Crigler-Najjar syndrome type 1: orthotopic liver transplantation (OLT) and auxiliary partial orthotopic liver transplantation (APOLT). [24]

### **Hepatocyte Transplantation**

Hepatocyte transplantation is a promising alternative to liver transplantation. It is a temporary method of reducing serum bilirubin levels, with published reports of a 50% reduction in bilirubin levels. Therefore, hepatocyte transplantation in patients with Crigler-Najjar syndrome is performed as a temporary therapeutic approach for patients awaiting whole organ transplantation. [28, 29] Therapies based on the transplantation of allogeneic hepatocytes or hepatocyte progenitor cells have the potential to cure inherited liver disorders. Transplantation of isolated allogeneic hepatocytes has been attempted in patients with Crigler-Najjar syndrome, but only limited and transient benefits have been achieved. [30, 31, 32]

### **Gene Therapy**

Gene therapy by gene replacement involves adding new genes to a patient's cells to replace missing or malfunctioning ones. The introduction of a normal UGT1A1 gene can potentially cure the genetic defect. This can be achieved through ex vivo gene transduction and vector-mediated gene delivery. Adenovirus is the most effectively used vector for gene transfer to

liver cells. Plans for clinical trials in humans are currently underway. [33]

## **Conclusions**

Crigler-Najjar syndrome is a rare, inherited metabolic disorder characterized by a complete or partial deficiency of the enzyme UDP-glucuronosyltransferase, caused by mutations in the UGT1A1 gene. This disorder leads to the accumulation of indirect bilirubin in the blood, resulting in severe neonatal jaundice. There are two types of the syndrome: type I, associated with a complete lack of the enzyme, and type II, where there is a partial enzyme deficiency. Type I often requires liver transplantation, while type II can be managed with phototherapy and medications such as phenobarbital. Diagnosis is based on genetic testing and clinical evaluation, including the analysis of bilirubin levels. Early diagnosis and treatment are crucial to prevent severe neurological complications, such as kernicterus, which can lead to permanent brain damage. In recent years, new therapeutic options have emerged, including gene therapies, offering hope for more effective treatment of this disease. Although the disease is not common, it poses a serious problem. However, the advancement of medicine gives reason to believe in the development of even more effective methods to combat the effects of the mutation causing it. This article presented a review of the current knowledge on Crigler-Najjar syndrome, covering its etiology, pathogenesis, clinical presentation, and modern diagnostic and treatment methods. The importance of further research and the development of new therapies to improve the quality of life for patients with this condition was also emphasized. Increasing clinical awareness among physicians of various specialties is essential to ensure proper care and support for patients and their families.

## **Disclosures**

The authors confirm that they have no financial or other conflicts of interest that could affect the interpretation of the research findings or the content of this manuscript. This study was conducted independently, without any external financial support or assistance.

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### **Conflicts of Interest**

The authors declare no conflict of interest.

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