IJMPR 2025, 9(2), 7-11

International Journal of Modern Pharmaceutical Research
www.ijmpronline.com

ISSN: 2319-5878
IJMPR
Review Article
SJIF Impact Factor: 6.669

CRIGLER-NAJJAR SYNDROME: A COMPREHENSIVE OVERVIEW OF CAUSES, CLINICAL FEATURES, AND MANAGEMENT APPROACHES

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Article Received on: 13/12/2024
Article Revised on: 02/01/2025
Article Accepted on: 23/01/2025

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ABSTRACT

Crigler-Najjar Syndrome (CNS) is a very rare autosomal recessive disorder. It is due to deficiency of the hepatic enzyme, uridine 5-diphosphate glucuronosyltransferase (UGT1A1), responsible for the conjugation of bilirubin, which leads to its accumulation in blood in the form of unconjugated. This condition often exhibit symptom like jaundice, and if not treated, may lead to severe neurological damage with the probability of kernicterus. The syndrome has two types, namely Type I, which has a complete enzyme deficiency and has a high risk of death in infancy, and Type II, which has partial enzyme activity and is less severe, allowing for survival despite persistent jaundice and pruritus. CNS is caused by mutations in the UGT1A1 gene located on chromosome 2q37. It has a rare incidence rate at an incidence rate of approximately 0.6 to 1 in 1 million live births. Genetic testing along with clinical evaluations establish a diagnosis of this disease. Main aims of treatments include decreasing levels of bilirubin as well as avoidance of neurological injuries. These involve the administration of phototherapy which further aids in degrading extra bilirubin produced, along with phenobarbitol used for boosting activity of UGT1A1. For severe cases, liver transplantation is considered the most effective treatment. Gene therapies also is another exciting area of study that might ensure a life-time cure as a result of gene replacement causing the disorder. Prompt diagnosis and management are key steps to an optimistic prognosis and enhancing the quality of life of these patients with Crigler-Najjar Syndrome.

KEYWORDS: Crigler-Najjar Syndrome, UGT1A1 deficiency, Unconjugated bilirubin, Jaundice, Kernicterus, Phototherapy, Liver transplantation.

INTRODUCTION

Crigler-Najjar Syndrome (CNS) is a rare autosomal recessive life-threatening disorder characterised by deficiency of hepatic microsomal bilirubin uridine 5′-diphosphate glucuronyltransferase (UGT1A1) enzyme that encodes the hepatic UDP-glucuronosyltransferase. This occurs when the bilirubin crosses the blood brain barrier and binds to specific tissues present in the brain. It was first identified in 1952 and termed by the two physicians named John Crigler and Victor Najjar.[1&2]

The various forms of CNS are Type I and Type II deficiency of of uridine 5′-diphosphate glucuronyltransferase (UGT1A1) enzyme. Type I is characterised by the complete loss of the function of the enzyme whereas the Type II is characterised by the partial loss of the function of the enzyme. Type I patients who affects with the disease may usually die in the infancy but patients affected with Type II survive despite long term Pruritis and Icterus.[1&2]

The major identification for CNS is Jaundice in which increased bilirubin levels (Hyperbilirubinemia) are seen.[3] Bilirubin is formed from the breakdown of RBC in the liver. Bilirubin is a yellowish- orange coloured pigment that enters the liver in unconjugated form which is not soluble in water is then undergoes a chemical reaction to convert into conjugated bilirubin which is water soluble that can be easily passed into small intestine. Severe unconjugated hyperbilirubinemia may lead to a condition called Bilirubin Encephalopathy(kernicterus) in which brain impairment occurs cauesd by the accumulation of unconjugated bilirubin that crossed the blood brain barrier in the brain.[4]

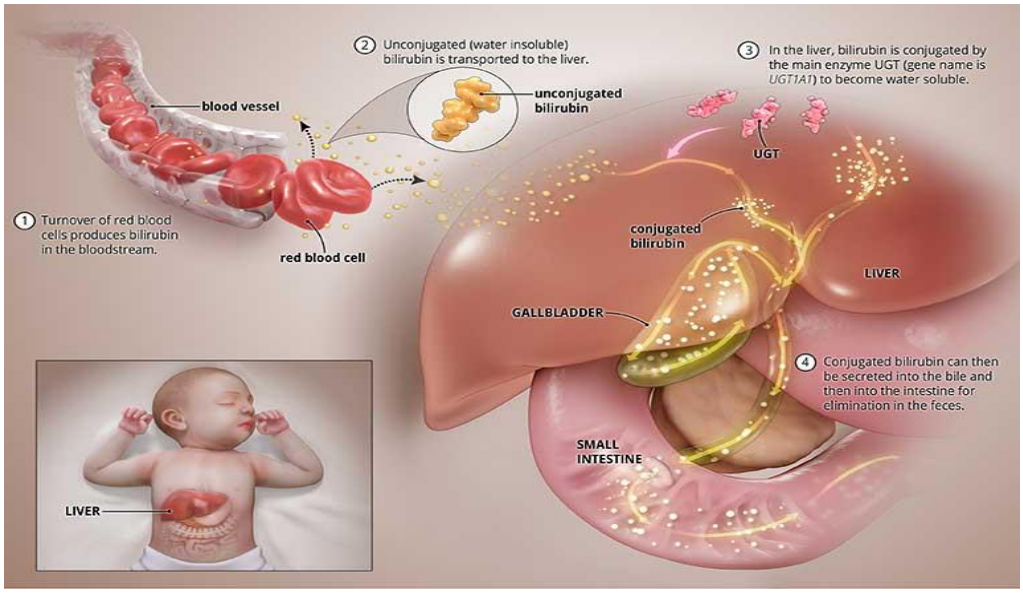

Figure 1.1: Describes the Mechanism of Crigler Najjar Syndrome.

EPIDEMOLOGY OF CRIGLER -NAJJAR SYNDROME (CNS)

Crigler-Najjar Syndrome is a rare disease in which only the affecting rate of this condition is 0.6 to 1 in 1 million of the newborn babies across the world who requires an urgent medical attention with a specialised care to face the consequences.[5]

CLASSIFICATION OF CRIGLER-NAJJAR SYNDROME(CNS)

On the basis of bilirubin uridine diphosphate glucuronosyl transferase (bilirubin-UGT) activity this CNS is classified into 2 types.[6]

Table 1.1: Describes the Types of CNS.

TYPE 1	TYPE 2
• Bilirubin-UGT is completely absent • No conjugated bilirubin is seen • Can be identified if plasma bilirubin Levels are >20mg/dl • Jaundice along with conjugated hyperbilirubinemia period • More likely to develop Bilirubin Encephalopathy	• Bilirubin-UGT is reduced but not completely absent • Decreased conjugated bilirubin level are seen • Usually <20mg/dl is seen • No ill is seen during neonatal period but seen in short period of time after birth • Less likely to develop Bilirubin Encephalopathy

ETIOLOGY OF CRIGLER-NAJJAR SYNDROME(CNS)

Crigler-Najjar Syndrome is a genetic disorder caused in the mutations of UGT1A1 gene on the chromosome2 q37 that results in the deficiency of bilirubin uridine diphosphate glucuronosyl transferase (bilirubin-UGT) enzyme present in the liver helps for the elimination of bilirubin present in the body by a process called glucuronidation. In this process the uncongugated bilirubin gets coverted to conjugated bilirubin for the excretion so that it can get completely eliminated from the body. If the glucuronidation reaction does not occurs the unconjugated bilirubin gets accumulated in the blood that leads to jaundice and unconjugated hyperbilirubinemia.[7]

RISK FACTORS OF CRIGLERS-NAJJAR SYNDROME

1. **Genetic Inheritence:** Autosomal Recessive Pattern – Mutations in the UGT1A1 gene is the primary cause.
2. **Family History:** Family History of Criglers- Najjar Syndrome or severe neonatal jaundice may raises the risk of Criglers – Najjar Syndrome.
3. **Parental Consaguinity:** Parents who are closely related by blood have a high chance of passing the mutated gene.
4. **Other Disorders:** A family history of other heriditary liver or bilirubin metabolism disorders might increase the risk of Criglers -Najjar Syndrome.[4]

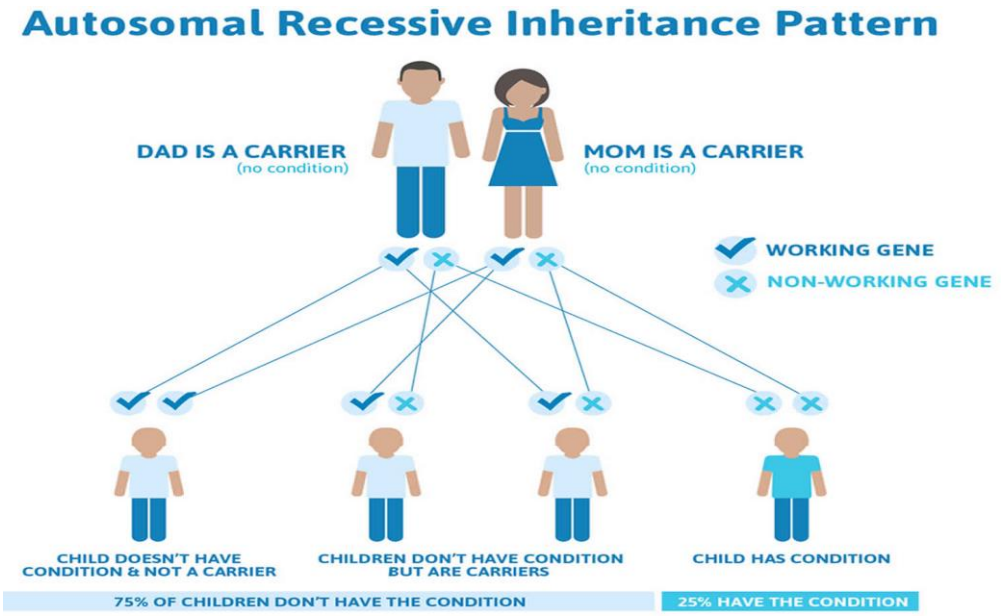

Figure 1.2: Shows the pattern of Inheritance of CNS.

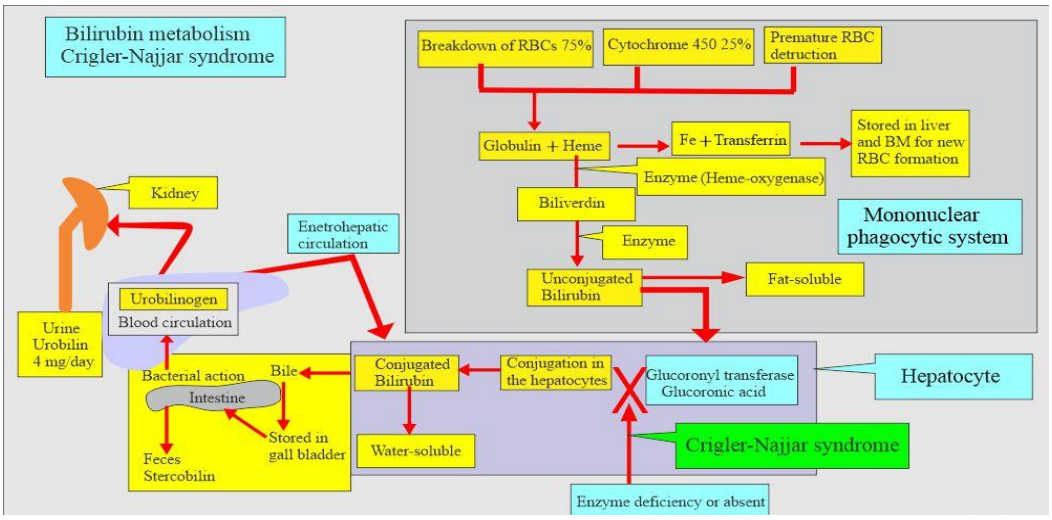

Figure 1.3: Describes the Pathophysiology of CNS.

CLINICAL FEATURES OF CRIGLER- NAJJAR SYNDROME

The main symptom of Crigler-Najjar Syndrome is Neonatal Jaundice in which yellowish tints to eyes and skin is seen which in turn causes Kernicterus. The symptoms of Kernicterus include.

- Muscle spasms
- Choreoathethosis (reduced motor activity)
- Difficulty in hearing
- Extereme fatigue
- Periods of weak muscle tone (hypotonia/hypertonia)
- Fever
- Improper Cognitive Functions.[3]

DIAGNOSIS

- Genetic Testing of UGT1A1 gene
- Computed Tomography
- Blood Test
- Faily History Collection
- Phenobarbitol Drug Testing to differentiate the type affected.[8]

MANAGEMENT

The main aim in treating the Criglers-Najjar syndrome is to decrease the unconjugated bilirubin levels of blood. There are some treatment strategies in treating this condition. Those are as follows.

1. Phototherapy
2. Phenobarbitol
3. Gene Therapy
4. Liver Transplantation

➢ Phototherapy

The phototherapy consists of a panel of ten foot, 40W special Billi Blue (BB) LED fluorescent tubes in a rigid, overhead, aluminum frame (66 × 137 cm). Newborns received 15-20 hours of phototherapy daily with 60%-70% of body surface exposed and light positioned 30-45 cm from the skin. For older children and adults, the light

source was typically placed 45-60 cm from the skin and delivered.[9]

Figure 1.4: shows the treatment of phototherapy in neonatal jaundice.

- **Phenobarbitol**

Phenobarbitol is used as basic treatment for treating the crigler-najjar syndrome which stops the acute increase in the levels of bilirubin and induces the uridine diphosphate glucuronosyltransferase (UDPGT) enzyme activity and improves bilirubin clearance by liver uptake for storage and excretion.[10]

Dose: 2 mg/kg/dose two–three times per day

- **Gene Therapy**

In gene therapy, the defective gene present in a patient is substituted with a gene encoding the hUGT1A1 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.[11]

- **Liver Transplantation**

It is the best option for treating the criglers-najjar syndrome that can improve the quality of life of patients The three types of liver transplantation used for treating patients are (1) Orthotopic Liver Transplantation (OLT), the most common approach, which involves replacing the entire native liver with a whole or partial graft from either a living or deceased donor; (2) Auxiliary Liver Transplantation (ALT), where a segment of the donor's liver is transplanted while retaining the patient's native liver; and (3) Auxiliary Partial Orthotopic Liver Transplantation (APOLT), which is similar to ALT, but only a partial liver graft is transplanted alongside the patient's own liver.[12]

DISCUSSSION

Crigler-Najjar Syndrome (CNS) is one of the rare genetic conditions caused due to the mutation in UGT1A1, an enzyme encoded gene, that helps in the facilitation of uridine 5′-diphosphate glucuronosyltransferase. The deficiency of UGT1A1 causes CNS because of the deficiency that can increase levels of unconjugated bilirubin and the accumulation process as well since the body excretion is hampered, and they cannot become water-solubility. Such is a by-product of red blood cells destruction. A defect in this enzyme causes a collection of unconjugated bilirubin within blood circulation. This leads to jaundice in CNS. If left untreated, kernicterus develops, including severe neurologic damage with deposition of bilirubin in brain tissue.

There are two classes differentiated according to enzyme deficiency severity of CNS. Type I presents completely with lack of activity for UGT1A1 and accompanied by very high bilirubin levels, often resulting in death at infancy due to bilirubin encephalopathy. The enzyme is partially active in the case of Type II, thus bringing about moderate hyperbilirubinemia. Type II patients can survive to adulthood but experience long-term sequelae like pruritus and persistent jaundice.

Diagnosis in CNS is done by genetic test to confirm mutation in the gene UGT1A1. Clinical presentation would include prolonged neonatal jaundice and more severe neurological presentation such as spasm, impairment of hearing and cognitive dysfunction. Blood tests may show elevated unconjugated bilirubin, whereas phenobarbitol testing may help differentiate Type I from Type II.

Treatment includes bringing down the level of bilirubin to avert kernicterus. Phototherapy is the treatment of choice since the light produced has been proven to facilitate the breakdown of unconjugated bilirubin. Phenobarbitol has the ability to induce activity in the UGT1A1 gene, thus enhancing the elimination of bilirubin. Severe cases have only one definite cure: that is liver transplantation. Gene therapy-the replacement of the defective gene-holds great promise for a long-term cure. Early diagnosis and intervention are critical in improving outcomes for CNS patients, and ongoing research into genetic and therapeutic interventions offers hope for more effective treatments in the future.

CONCLUSION

Crigler-Najjar Syndrome is a rare disorder but has the potential to bring disastrous complications if not diagnosed early and managed appropriately. The disease itself does not have a proper cure, but methods of treatment can exist in the form of phototherapy, phenobarbitol, and even liver transplantation that will ensure an improved quality of life for the patients. Gene therapy might one day provide a permanent solution for them. With increased awareness and advancement in genetic medicine, patients with Crigler-Najjar Syndrome can now expect better outcomes, and the early detection and intervention are crucial for better patient care.

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