



## Crigler Najjar Syndrome - A Rare case of Jaundice in Children

**B Naher<sup>1</sup>, M W Mazumder<sup>2</sup>, S Ghosal<sup>3</sup>, M Benzamin<sup>4</sup>, A Z M R Rahman<sup>5</sup>  
A S M B Karim<sup>6</sup>**

### Abstract

Crigler-Najjar syndrome (CNS) was first described in 1952 in Maryland, USA as congenital familial non-hemolytic jaundice with kernicterus by Crigler JF and Najjar VA.<sup>1</sup> CNS is a rare genetic disorder characterized by abnormalities in bilirubin metabolism and evident by persistent increase of unconjugated bilirubin.

During the first days of life, the syndrome clinically manifests as intense unconjugated hyperbilirubinemia without evidence of hemolysis. It consists of two types, type I and type II. Crigler-Najjar Syndrome is mostly autosomal recessive disorder, but variation may occur in the inheritance of CNS II.<sup>2</sup> The key pathogenesis is defect in bilirubin conjugation due to complete or partial deficiency of uridine 5'-diphosphate-glucuronosyl transferase (UGT). This enzyme is required for the conjugation and further excretion of bilirubin from the body. In type I CNS the enzyme activity is completely absent and in type II there is partial absence of the enzyme. Therefore, Type I is more severe form and usually fatal with kernicterus at the age of 1-2 years.<sup>3-5</sup> Type II is less severe and has better prognosis. Patients with CN type II suffer from less jaundice, less neurological impairment, and show a fair response to phenobarbitone therapy (serum bilirubin levels decrease by at least 25%).<sup>6</sup>

Both males and females are equally affected by CNS. The incidence is approximately 1 in 750,000-1,000,000 in the general population.<sup>7</sup> Here we report such a rare case.

DOI: <https://doi.org/10.3329/nimcj.v12i1.61594>

Northern International Medical College Journal Vol. 12 No. 1 July 2020, Page 515-517

<sup>1</sup> Dr. Bodhrun Naher  
MD Phase B Resident  
Dept. of Pediatric  
Gastroenterology and Nutrition  
Bangabandhu Sheikh Mujib  
Medical University (BSMMU),  
Dhaka

<sup>2</sup> Dr. Md. Wahiduzzaman Mazumder  
Associate Professor

<sup>3</sup> Dr. Sharmistha Ghosal  
MD Phase B Resident

<sup>4</sup> Dr. Md. Benzamin  
MD Phase B Resident

<sup>5</sup> Dr. A Z M Raihanur Rahman  
MD Phase B Resident

<sup>6</sup> Dr. A S M Bazlul Karim  
Professor

1, 2, 3, 4, 5, 6  
Dept. of Pediatric Gastroenterology  
and Nutrition  
Bangabandhu Sheikh Mujib Medical  
University (BSMMU), Dhaka

Correspondence  
Dr. Bodhrun Naher  
MD Phase B Resident  
Dept. of Pediatric Gastroenterology  
and Nutrition  
Bangabandhu Sheikh Mujib Medical  
University (BSMMU), Dhaka  
E-mail: drmd.benzamin@yahoo.com

### Case Report

Arafat, a 13-months-old male baby, only issue of a consanguineous parents, admitted into the Paediatrics department, BSMMU, Dhaka with the complaints of jaundice since birth. There was no history of fatigability, fever, abdominal pain, pruritus, clay colored stools or dark colored urine.

Physical examination revealed only severe jaundice but no other abnormal findings became apparent. There was no pallor, hepatosplenomegaly or any feature of liver cirrhosis.

Complete blood count showed normal hemoglobin, adequate platelet count and no evidence of hemolysis. Reticulocyte count was within normal limit. Osmotic fragility test was normal, and Coombs' test was negative. Thyroid function was within normal range. Screening for

antibodies of toxoplasmosis, rubella, and cytomegalovirus infections found negative.



Abdominal ultrasonography did not show any abnormality. Liver function test showed- total



serum bilirubin 16.75 mg/dl (conjugated bilirubin 0.52 mg/dl and un-conjugated bilirubin 16.23mg/dl), alanine amino transferase 34 IU/L,

aspartate amino transferase 26IU/L, alkaline phosphatase 387 U/L, albumin 3.8 g/dL, Prothrombin time 14.40 seconds, INR 1.21.

The persistent unconjugated hyperbilirubinemia in the absence of hemolysis and liver dysfunction suggests Crigler-Najjar syndrome. As genetic mutation analysis for CNS is not available in Bangladesh we directly went for treatment. We started treatment with oral phenobarbitone 5mg /kg/day twice daily and advised him to come for follow up after 2 weeks. During follow up we found sharp decreased of serum bilirubin level to 11.9 mg/dl. Follow up After 1 month we found further decreased serum bilirubin level. It was 6.6 mg/dl where indirect bilirubin level was 6.2 mg/dl. All these responses of indirect hyperbilirubinaemia on phenobarbitone therapy boosted the diagnosis of Crigler-Najjar syndrome type II in this case.

### Discussion

Hereditary hyperbilirubinemias are the direct result of genetic defects in enzymes that control the bilirubin metabolism. Having two major types of hereditary hyperbilirubinemias; the unconjugated hyperbilirubinemia such as CNS (type I,II), Gilbert syndrome (GS) and the conjugated hyperbilirubinemia such as Dubin-Johnson syndrome and Rotor syndrome.<sup>8</sup>

CNS (I, II ) and GS resulted from genetic mutations of UGT1A1 (which transforms the un-conjugated bilirubin in to a nontoxic form by inserting one glucuronic acid). Genetic mutations of UGT1A1 results in absence, severe or moderate reduction of UGT1A1 enzymatic activities (corresponding to CNS-I, CNS-II or GS disease respectively.<sup>9</sup> The clinical classifications of CNS-I, CNS-II and GS are based on several parameters such as the bilirubin levels, the presence or absence of kernicterus, and the response to phenobarbitone therapy.

The symptoms of CNS I is jaundice which is severe, persistent and starts shortly after birth. Bilirubin level of CNS-I patients is above 30mg/dL or higher and due to the complete absence of UGT1A1 enzyme activity and patients do not respond to the Phenobarbitone therapy. Kernicterus develops within first month of life and causes early death of the infant. CNS II is milder form than CNS I. There is also persistent jaundice. Serum bilirubin in CNS II is usually up to 20mg/dl or even more during intercurrent illness, prolonged fasting or by general anesthesia.<sup>11</sup> Some patients may not be diagnosed until adulthood. Kernicterus is rare in CNS II.

In Gilbert syndrome serum bilirubin level rarely exceeds 6 mg/dl.<sup>10</sup> The first clue of CNS is persistent indirect hyperbilirubinaemia. Hemolytic anaemia should be excluded to

diagnose CNS. For confirmation of the diagnosis molecular genetic testing is required which can detect mutations in the UGT1A1 gene that causes the disease. But this requires highly specialized laboratories which is not available everywhere.

Therefore, to differentiate CNS I, II and Gilbert syndrome the most reasonable approach is phenobarbitone trial. Phenobarbitone, a barbiturate, reduces serum bilirubin levels in individuals affected with CNS II and Gilbert syndrome, but is ineffective for those with CNS I. Administration of phenobarbitone completely normalizes the bilirubin levels in Gilbert's Syndrome.<sup>11</sup>

But in CNS II the fall in bilirubin level is usually more than 25 percent, but the level never be normal. The fall is almost nil in CNS I. In CNS type II, the response with phenobarbitone is due to induction of the already present residual 10%-30% of (UGTA) enzyme activity required for bilirubin conjugation. Therefore, failure to respond to phenobarbitone is an important point in differential diagnostic purpose.

Treatment goal of CNS is lowering the unconjugated bilirubin level. The cornerstone of treatment for CNS I is aggressive phototherapy to prevent development of kernicterus during the first few months of life. As CNS II is milder and responds very well to phenobarbitone therapy and therefore lifelong treatment with this drug is advised. The dose of phenobarbitone is 3-5 mg/kg/day in divided doses.<sup>11</sup> The response is observed after two to three weeks therapy. In addition, calcium supplementation has also been found to increase the gut excretion of bilirubin. During an episode of a hyperbilirubinemia crisis, patients with CNS II may require phototherapy or plasma pheresis. Newer therapeutic modalities such as hepatocyte transplantation, enzyme replacement therapy (ERT) and gene therapy have not been used for CNS II till date. As the affected patients respond well on oral phenobarbitone only.

For the affected individuals and their families, genetic counseling is recommended. Psychological support is essential as well. In our case, the 13 months old boy, has the history of jaundice since birth and investigations showed persistently raised indirect hyperbilirubinaemia. Hemolysis was excluded by doing relevant blood tests. We tried phenobarbitone trial to see the response as there was no facility of doing the genetic testing to identify mutations of UGT1A1 gene in Bangladesh. After administration of phenobarbitone serum bilirubin level sharply declined within next few weeks from 16.5 mg/dl to 11.9 mg/dl and finally 6mg/dl which otherwise confirms the diagnosis of CNS II.

**(Permission taken from the parents of the patient to publish the case history and photo)**

## References

1. Crigler, J. F., and V. A. Najjar. 1952. Congenital familial nonhemolytic jaundice with kernicterus. *Pediatrics* 10 : 169-180. Radlovic N. Hereditary hyperbilirubinemias. *Srpskiarhiv za celokupnolekarstvo*. 2014;142(3-4):257-60.
2. Radlovic N. Hereditary hyperbilirubinemias. *Srpskiarhiv za celokupnolekarstvo*. 2014;142(3-4):257-60.
3. Van der Veere CN, Sinaasappel M, McDonagh AF, Rosenthal P, Labrune P, Odièvre M, et al. Current therapy for Crigler-Najjar syndrome type 1: Report of a world registry. *Hepatology*. 1996;24(2):311-15.
4. Hafkamp A, Nelisse-Haak R, Sinaasappel M, Oude Elferink RP, Verkade HJ. Orlistat Treatment of unconjugated hyperbilirubinemia in Crigler-Najjar disease: a randomized controlled trial. *Pediatric Research*. 2007;62(6):725-30.
5. Nair KM, Lohse P, Nampoothiri S. Crigler-Najjar syndrome type 2: Novel UGT1A1 mutation. *Indian Journal of Human Genetics*. 2012;18(2):233-34.
6. Ranjan P, Kohli S, Saxena R, Thakur S. Mutation analysis in Crigler-Najjar Syndrome type ii—case report and literature review. *Journal of Clinical and Experimental Hepatology*. 2011;1(3):204-06.
7. Kadakol A, Ghosh SS, Sappal BS, Sharma G, Chowdhury JR, Chowdhury NR. Genetic lesions of bilirubin uridine-diphosphoglucuronate glucuronosyltransferase (UGT1A1) causing Crigler-Najjar and Gilbert syndromes: correlation of genotype to phenotype. *Hum Mutat*. 2000;16(4): 297–306.
8. Passuello V, Puhl AG, Wirth S, Steiner E, Skala C, Koelbl H, et al., Pregnancy outcome in maternal Crigler-Najjar syndrome type II: a case report and systematic review of the literature. *Fetal Diagn Ther*. 2009;26:121-26.
9. Pett S, Mowat AP. Crigler-Najjar syndrome types I and II. Clinical experience - King's College Hospital 1972-1978. Phenobarbitone, phototherapy and liver transplantation. *Mol Aspects Med*. 1987;9(5):473–82.
10. Maruo Y, Nakahara S, Yanagi T, Nomura A, Mimura Y, Matsui K, Sato H, Takeuchi Y. Genotype of UGT1A1 and phenotype correlation between Crigler-Najjar syndrome type II and Gilbert syndrome. *J Gastroenterol Hepatol*. 2016;31(2):403–8.
11. Passuello V, Puhl AG, Wirth S, Steiner E, Skala C, Koelbl H, Kohlschmidt N. Pregnancy outcome in maternal Crigler-Najjar syndrome type II: a case report and systematic review of the literature. *Fetal Diagn Ther*. 2009;26(3):121–6.



**Dr. Bodhrun Naher**, completed her MBBS from Dhaka Medical College. After that she did her post-graduation in Pediatrics (MCPS And FCPS). She is doing Govt. service and her current designation is junior consultant ( Pediatrics). She is currently posted at BSMMU on deputation.