International Journal of Contemporary Pediatrics
*Pereira DL et al. Int J Contemp Pediatr. 2026 Jun;13(6):1018-1021*
https://www.ijpediatrics.com
pISSN 2349-3283 | eISSN 2349-3291

DOI: https://dx.doi.org/10.18203/2349-3291.ijcp20261552

**Case Report**

# A rare case of Crigler–Najjar syndrome type II in a preterm infant: clinical, genetic and therapeutic insights into the UGT1A1 Pro176Leu variant

**Darren L. Pereira*, Ataah S. Qureshi**

MGM Medical College and Hospital, Kamothe, Navi Mumbai, Maharashtra, India

**Received:** 22 February 2026
**Revised:** 18 March 2026
**Accepted:** 07 May 2026

***Correspondence:**
Darren L. Pereira,
E-mail: backup4darren@gmail.com



## ABSTRACT

Crigler–Najjar syndrome type II is a rare autosomal recessive disorder caused by partial deficiency of uridine diphosphate-glucuronosyltransferase (UGT1A1), resulting in unconjugated hyperbilirubinemia. Differentiating Crigler–Najjar syndrome type II from common neonatal jaundice can be challenging, particularly in premature infants, yet early diagnosis is critical to prevent bilirubin-induced neurotoxicity. We report a 32-week preterm male neonate presenting with progressive jaundice, with peak total serum bilirubin reaching 24 mg/dl. Hemolysis and hepatic dysfunction were excluded through laboratory evaluation. Genetic analysis was performed to identify underlying enzymatic defects. The infant was managed with intensive blue-light phototherapy and phenobarbital at a dose of 5 mg/kg/day, with serial bilirubin monitoring. Genetic testing demonstrated a homozygous UGT1A1 Pro176Leu mutation, confirming Crigler–Najjar syndrome type II. Following initiation of therapy, serum bilirubin levels declined by approximately 25% within one week, consistent with typical Crigler–Najjar syndrome type II responsiveness to phenobarbital. The neonate exhibited no clinical features of kernicterus, and bilirubin levels stabilized below 15 mg/dl by day 12 of life. This case underscores the diagnostic difficulty of distinguishing Crigler–Najjar syndrome type II from physiological or prematurity-related jaundice. Identification of the rarely reported Pro176Leu variant in a preterm neonate provides additional genetic and developmental insight. Early recognition, prompt initiation of phototherapy, phenobarbital therapy, and caregiver education remain essential to prevent bilirubin-induced neurological injury.

**Keywords:** Crigler-Najjar syndrome type 2, Unconjugated hyperbilirubinemia, Neonatal jaundice

## INTRODUCTION

Crigler–Najjar syndrome represents one of the most clinically important hereditary disorders of bilirubin conjugation. It results from mutations in UGT1A1, the gene encoding bilirubin uridine diphosphate-glucuronosyltransferase, the enzyme responsible for converting hydrophobic unconjugated bilirubin into water-soluble conjugated bilirubin.[1] In Crigler–Najjar syndrome type I, enzyme activity is virtually absent, causing severe, persistent hyperbilirubinemia and a complete lack of response to phenobarbital. By contrast, Crigler–Najjar syndrome type II is characterized by residual UGT1A1 activity typically less than 10% of normal allowing partial bilirubin conjugation. Patients with Crigler–Najjar syndrome type II usually exhibit moderately elevated bilirubin levels, often in the 5–25 mg/dl range, and unlike Crigler Najjar Syndrome type I, they show a predictable reduction in bilirubin when treated with phenobarbital due to hepatic enzyme

induction. Neonates, especially those born prematurely, are uniquely vulnerable to disorders of bilirubin metabolism because their hepatic conjugation pathways are immature. Nearly 80% of preterm infants develop some degree of jaundice during the first week of life. In this context, the early clinical picture of Crigler–Najjar syndrome type II may closely resemble more common causes of neonatal hyperbilirubinemia such as physiologic jaundice, breast milk jaundice, hemolytic anaemia, or neonatal sepsis.[2] Standard diagnostic evaluation must therefore rule out hemolytic conditions, blood-group incompatibilities, G6PD deficiency, and infectious etiologies before rare metabolic causes are considered. When jaundice persists despite normal haemolysis markers and normal liver function tests, a hereditary disorder such as Crigler–Najjar syndrome type II should rise on the differential list.

Differentiating Crigler–Najjar syndrome type II from other UGT1A1-related syndromes is essential.[3] Gilbert syndrome, for example, results from promoter variants that reduce but do not abolish enzyme expression and typically produces mild, episodic unconjugated hyperbilirubinemia with levels rarely exceeding 5 mg/dl. Crigler–Najjar syndrome type II, in contrast, presents with higher bilirubin levels and carries a real, though smaller than Crigler–Najjar syndrome type I, risk of kernicterus.[4] Early identification has therapeutic implications: phototherapy and phenobarbital are effective in Crigler–Najjar syndrome type II but insufficient in Crigler–Najjar syndrome type I, where interventions such as plasmapheresis or even liver transplantation may be required.[5] Genetic analysis therefore plays a crucial role in confirming the diagnosis and guiding clinical decision-making, particularly in distinguishing Crigler–Najjar syndrome type II from Crigler–Najjar syndrome type I, where phenobarbital responsiveness is absent.[6,7]

## CASE REPORT

A male neonate was born at 32 weeks of gestation weighing 1.8 kg following an uncomplicated spontaneous vaginal delivery. Apgar scores were 7 and 9 at one and five minutes. Jaundice became clinically apparent on day 3 of life. By day 5, total serum bilirubin rose rapidly from an initial 12 mg/dl to 24 mg/dl, predominantly unconjugated. The infant displayed mild lethargy and feeding intolerance, raising concern for evolving bilirubin neurotoxicity.

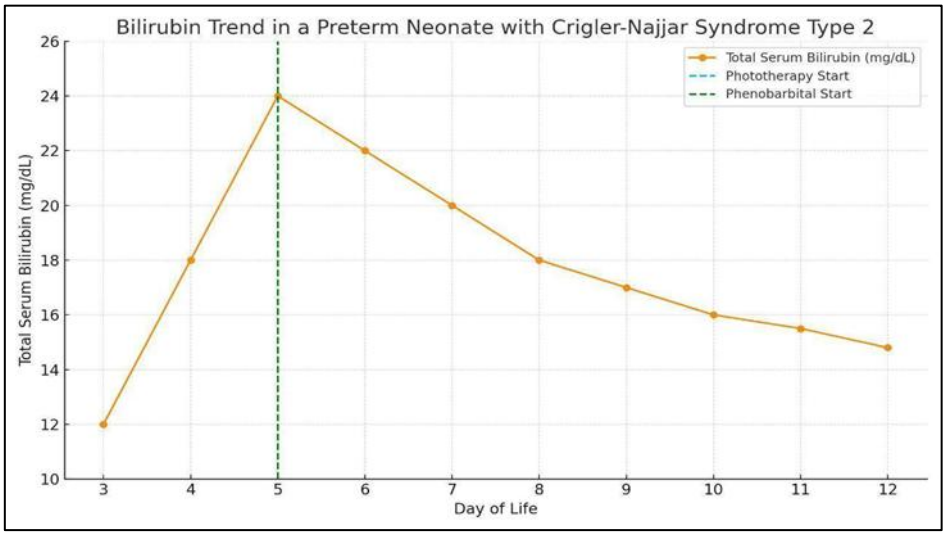


**Figure 1: Bilirubin Trend.**

Extensive laboratory evaluation revealed no evidence of haemolysis: the complete blood count was normal, the peripheral smear showed no schistocytes or spherocytes, the direct Coombs test was negative, and G6PD levels were normal.[8] Liver transaminases and albumin levels remained within neonatal reference ranges. With common causes excluded and bilirubin rising disproportionately, a genetic etiology was suspected.[9]

Targeted sequencing of UGT1A1 identified a homozygous c.526C>T (p.Pro176Leu) missense mutation, confirming Crigler–Najjar syndrome type II. This variant, previously described as novel, had not been reported in a preterm neonate, raising important developmental questions about the interaction between prematurity and genetically impaired bilirubin metabolism.[10]

Therapeutically, intensive blue-light phototherapy was initiated immediately upon diagnosis and continued nearly continuously from day 5 to day 9, then gradually tapered. Phenobarbital was administered at 5 mg/kg/day (approximately 2 mg/kg every 8 hours), a regimen consistent with neonatal induction protocols. Supportive NICU measures included thermoregulation, controlled stimulation, adequate hydration, and optimized nutrition to promote bilirubin elimination. The infant demonstrated a clear therapeutic response. After one week, bilirubin

had decreased by approximately 25%, consistent with expected Crigler–Najjar syndrome type II behavior.[11] By day 12, Total Serum Bilirubin stabilized below 15 mg/dl, and no neurological signs of acute bilirubin encephalopathy were observed (Figure 1). Although weight declined to 1.2 kg during the first week due to illness and prematurity, it improved to 1.4 kg by discharge. Follow-up showed an uneventful recovery was achieved, with due compliance.

## DISCUSSION

The clinical presentation of Crigler–Najjar syndrome type II in a preterm neonate creates a diagnostic intersection between a rare genetic enzyme deficiency and the common physiological immaturity of the liver. To better understand the implications of this case, we compare our specific findings against established literature across four key parameters:

### *Gestational age and prematurity*

Premature infants are naturally predisposed to jaundice due to immature conjugation pathways and reduced albumin binding. While approximately 80% of preterm infants develop jaundice, the rapid rise to a peak of 24 mg/dl in this 32-week neonate is atypical. Similar cases of severe neonatal hyperbilirubinemia have been documented, but often in the context of other variants like P364L.[12] Our case suggests that the Pro176Leu variant may exacerbate the developmental lag of hepatic enzymes in preterm infants more severely than in term neonates.

### *Magnitude of hyperbilirubinemia and neurotoxicity risk*

In Crigler–Najjar syndrome type II, total serum bilirubin typically ranges from 5 to 25 mg/dl. Our patient's peak of 24 mg/dl falls at the extreme high end of this spectrum. In contrast, Gilbert syndrome rarely exceeds 5 mg/dl. While the risk of kernicterus is significantly higher in Crigler–Najjar syndrome type I, this case mirrors findings that Crigler–Najjar syndrome type II patients remain vulnerable to neurological injury during periods of physiological stress such as prematurity and the associated 1.2 kg weight seen here.

### *Genetic variant comparison (Pro176Leu)*

The homozygous c.526C>T (p. Pro176Leu) mutation identified in this infant is a rarely reported variant in the UGT1A1 gene. Previous literature has characterized this variant as novel, but its specific behavior in a 32-week preterm setting has not been extensively documented.[13] Comparing this to the more common promoter variants found in Gilbert syndrome, the Pro176Leu missense mutation appears to cause a more profound reduction in residual enzyme activity, bringing the phenotype closer to the threshold of Crigler–Najjar syndrome type I .The identification of the Pro176Leu variant in a preterm neonate adds meaningful insight to the spectrum of UGT1A1 mutations.[14] Prematurity may amplify the phenotypic expression of partial enzymatic deficiencies, temporarily reducing bilirubin clearance below what might be seen in a term infant with the same genotype. This hypothesis warrants further research, particularly in populations with high prematurity rates.

### *Therapeutic response to phenobarbital*

A hallmark of Crigler–Najjar syndrome type II is a 20–30% reduction in Total Serum Bilirubin following phenobarbital administration. Our patient exhibited a 25% decline within one week. This aligns perfectly with expected therapeutic benchmarks for Crigler–Najjar syndrome type II and serves as a critical diagnostic differentiator from Crigler–Najjar syndrome type I, where phenobarbital response is entirely absent. Our dosing of 5 mg/kg/day was consistent with established neonatal induction protocols used in similar case studies. Phototherapy serves as the first-line treatment by converting bilirubin into excretable photo isomers. In Crigler–Najjar syndrome type II specifically, phenobarbital is a cornerstone therapy because it induces UGT1A1 expression and increases the conjugation capacity of the partially functioning enzyme. The typical 20–30% bilirubin reduction observed with phenobarbital serves not only as treatment but also as a diagnostic indicator that distinguishes Crigler–Najjar syndrome type II from Crigler–Najjar syndrome type I.

Experimental therapies including metalloporphyrins to inhibit heme oxygenase and bile acid sequestrants to reduce enterohepatic recycling have shown potential but remain limited by neonatal safety concerns.[15] Gene therapy using adeno-associated viral vectors is emerging as a future option, though not yet available for newborns. For now, Crigler–Najjar syndrome type II is generally manageable with established methods, as demonstrated in this case.

The primary risk associated with untreated Crigler–Najjar syndrome type II is kernicterus, caused by unbound unconjugated bilirubin crossing the blood–brain barrier and depositing in basal ganglia and brainstem nuclei. Although the risk is lower than in Crigler–Najjar syndrome type I, Crigler–Najjar syndrome type II patients can develop neurological injury under stressors such as dehydration, sepsis, or rapid bilirubin rises. Therefore, timely diagnosis and aggressive management remain essential. Care does not end with bilirubin stabilization. Long-term management requires multidisciplinary follow-up, caregiver education, and monitoring for developmental outcomes.

## CONCLUSION

Crigler–Najjar syndrome type II should be considered in any neonate, particularly a preterm infant with severe unconjugated hyperbilirubinemia that remains

unresponsive to routine measures. Early genetic confirmation is pivotal because it defines prognosis, guides the use of phenobarbital, and prevents unnecessary escalation to invasive procedures such as liver transplantation or plasmapheresis.

The present case demonstrates the characteristic phenobarbital responsiveness of Crigler–Najjar syndrome type II and expands clinical recognition of the Pro176Leu mutation. This case also highlights the developmental synergy between prematurity and genetic enzyme deficiencies. Greater awareness of rare metabolic causes of jaundice, combined with improved access to molecular diagnostics and consistent caregiver follow-up, is essential to prevent avoidable cases of bilirubin-induced neurological injury. Early genetic confirmation is pivotal because it defines prognosis, guides the use of phenobarbital, and prevents unnecessary escalation to invasive procedures. The present case demonstrates the characteristic phenobarbital responsiveness of Crigler–Najjar syndrome type II and expands clinical recognition of the Pro176Leu mutation. Greater awareness of rare metabolic causes of jaundice and improved access to molecular diagnostics will help prevent avoidable cases of bilirubin-induced neurological injury.

*Funding: No funding sources*
*Conflict of interest: None declared*
*Ethical approval: Not required*

## REFERENCES

1. You JY, Xiong LY, Wu MF, Fan JS, Fu QH, Qiu MH. Genetic variation features of neonatal hyperbilirubinemia caused by inherited diseases. World J Clin Pediatr. 2024;13(4):98462.
2. Singh A, Koritala T, Jialal I. Unconjugated Hyperbilirubinemia. In: StatPearls. Treasure Island (FL): StatPearls Publishing. 2025.
3. Rijal D, Rijal P, Bohare SM, Chaudhari AS, Dhungel M, Agarwal M, et al. A rare case of Crigler-Najjar syndrome type 2: A case report and literature review. Clin Case Rep. 2023;11(11):e8176.
4. Creeper K, Graham D. Crigler-Najjar type II in pregnancy: A case report. Obstet Med. 2023;16(3):184-6.
5. Lodoso Torrecilla B, Palomo Atance E, Camarena Grande C, Díaz Fernández MC, Hierro Llanillo L, De la Vega Bueno A, et al. Síndrome de Crigler-Najjar: diagnóstico y tratamiento. Pediatr (Barc). 2006;65(1):73-8.
6. Maruo Y, Nakahara S, Yanagi T, Nomura A, Mimura Y, Matsui K, et al. Genotype of UGT1A1 and phenotype correlation between Crigler-Najjar syndrome type II and Gilbert syndrome. J Gastroenterol Hepatol. 2016;31(2):403-8.
7. Cozzi L, Nuti F, Degrassi I, Civeriati D, Paolella G, Nebbia G. Gilbert or Crigler-Najjar syndrome? Neonatal severe unconjugated hyperbilirubinemia with P364L UGT1A1 homozygosity. Ital J Pediatr. 2022;48(1):59.
8. Wagner KH, Shiels RG, Lang CA, Seyed Khoei N, Bulmer AC. Diagnostic criteria and contributors to Gilbert's syndrome. Crit Rev Clin Lab Sci. 2018;55(2):129-39.
9. Canu G, Minucci A, Zuppi C, Capoluongo E. Gilbert and Crigler Najjar syndromes: an update of the UDP-glucuronosyltransferase 1A1 (UGT1A1) gene mutation database. Blood Cells Mol Dis. 2013;50(4):273-80.
10. Watchko JF. Review of the contribution of genetic factors to hyperbilirubinemia and kernicterus risk in neonates: a targeted update. Pediatr Med. 2021;4:7.
11. Nair KM, Lohse P, Nampoothiri S. Crigler-Najjar syndrome type 2: Novel UGT1A1 mutation. Indian J Hum Genet. 2012;18(2):233-4.
12. Jesus Sá C, Vilar Queirós R, Pessoa T, Santos S, Castilho S. Between Crigler-Najjar Syndrome Type II and Gilbert Syndrome: Expanding the Spectrum of Uridine Diphosphate Glucuronosyltransferase 1A1 (UGT1A1)-Related Hyperbilirubinemia. Cureus. 2026;18(1):e100926.
13. Hu RT, Wang NY, Huang MJ, Huang CS, Chen DS, Yang SS. Multiple variants in UGT1A1 gene are factors to develop indirect hyper-bilirubinemia. Hepatobiliary Surg Nutr. 2014;3(4):194-8.
14. Lee ZM, Chang LS, Kuo KC, Lin MC, Yu HR. Impact of Protein Binding Capacity and Daily Dosage of a Drug on Total Serum Bilirubin Levels in Susceptible Infants. Children (Basel). 2023;10(6):926.
15. Sambati V, Laudisio S, Motta M, Esposito S. Therapeutic Options for Crigler-Najjar Syndrome: A Scoping Review. Int J Mol Sci. 2024;25(20):11006.

**Cite this article as:** Pereira DL, Qureshi AS. A rare case of Crigler–Najjar syndrome type II in a preterm infant: clinical, genetic and therapeutic insights into the UGT1A1 Pro176Leu variant. Int J Contemp Pediatr 2026;13:1018-21.