APGHN
Archives of Pediatric Gastroenterology, Hepatology, and Nutrition

Case Report

Treatment of Severe Unconjugated Hyperbilirubinemia with Phenobarbitone in Two First-Degree Siblings with Crigler-Najjar Syndrome (CNS) Type 2: A Success Story

Sachin Kumar[1], Siddhavatam Rahul Karthik[1], Gandharav Pahuja[1], Sarthak Chakrabarti[1], Prateek Kumar Panda[1], Indar Kumar Sharawat[1]

[1]Department of Paediatrics, All India Institute of Medical Sciences, Rishikesh, Uttarakhand, India

e-ISSN: 2830-5442

Corresponding author:
Sarthak Chakrabarti
sarthakchakrabarti@gmail.com

Published:
30th November 2025

DOI:
https://doi.org/10.58427/apghn.4.4.2025.201-207

Citation:
Kumar S, Karthik SR, Pahuja G, Chakrabarti S, Panda PK, Sharawat IK. Treatment of severe unconjugated hyperbilirubinemia with phenobarbitone in two first-degree siblings with crigler-najjar syndrome (cns) type 2: a success story. *Arch Pediatr Gastr Hepatol Nutr*. 2025;4(4): 201-207

Abstract:

Background: Crigler–Najjar syndrome (CNS) type 2 is a rare autosomal recessive disorder of bilirubin conjugation caused by mutations in the *UGT1A1* gene. It presents in infancy with unconjugated hyperbilirubinemia that does not respond to phototherapy but improves with phenobarbitone, which enhances residual enzyme activity. Although phenobarbitone remains the cornerstone of treatment, familial recurrence of CNS type 2 is rarely reported in pediatric literature.

***Case*:** We report two siblings born to consanguineous parents who presented with progressive jaundice during early infancy. The first child, a 2-month-old boy, had multiple hospitalisations for phototherapy without benefit. Laboratory evaluation revealed total bilirubin of 31 mg/dL with normal liver function and no evidence of hemolysis. Genetic testing confirmed a homozygous *UGT1A1* (c.1456T>G; p.Tyr486Asp) mutation. He was treated with phenobarbitone (5–8 mg/kg/day) and calcium phosphate, achieving a bilirubin level <10 mg/dL within 4 weeks. Three years later, his younger sister developed similar unconjugated jaundice from day 4 of life and harboured the same mutation; she responded well to phenobarbitone alone. Both siblings remain well on long-term follow-up.

***Discussion*:** This case highlights the genetic basis and favorable response of CNS type 2 to phenobarbitone, which induces hepatic UGT1A1 expression. Familial clustering of CNS 2, though reported in few global studies, is seldom documented from India.

Conclusion: Early genetic diagnosis, timely institution of phenobarbitone, and family counselling are critical for successful management of CNS type 2. These cases reaffirm the long-term safety and efficacy of phenobarbitone in familial presentations of this rare disorder.

Keywords: crigler-najjar syndrome type 2, gene therapy, neonatal jaundice, phenobarbitone

Introduction

Crigler-Najjar syndrome (CNS) is a rare genetic disorder that affects the metabolism of bilirubin. It arises from mutations in the *UGT1A1* gene, which produces the enzyme uridine diphosphate glucuronosyltransferase (*UGT1A1*). When this enzyme is deficient, bilirubin cannot be conjugated properly, resulting in unconjugated hyperbilirubinemia from early infancy. There are two recognised types of CNS: type 1 has a complete enzyme deficiency and causes severe neonatal jaundice, which can progress to kernicterus without liver transplantation (LT). Type 2 has partial enzyme activity, allowing individuals to survive into adulthood, but with significant morbidity.[1, 2]

Clinically, infants with CNS present with persistent jaundice that does not respond to standard phototherapy. Type 1 typically shows serum bilirubin levels greater than 20–45 mg/dL and does not respond to phenobarbitone. In contrast, type 2 patients have bilirubin levels between 6–20 mg/dL and show a decrease in levels with phenobarbitone therapy.[3] Phenobarbitone, a barbiturate that helps induce the enzyme activity of the *UGT1A1* enzyme, remains the mainstay of treatment in CNS type 2. It increases the transcription of *UGT1A1*, which boosts the body's ability to process bilirubin and lowers serum bilirubin by 30-60 %.[4, 5] The use of phenobarbitone in pediatric type 2 CNS has been well-documented, showing long-term safety and effectiveness.[6]

Other treatments, like calcium phosphate, may also help reduce bilirubin by binding it in the gut and lowering enterohepatic circulation. Additional options include intensive phototherapy, plasmapheresis, exchange transfusions during emergencies, and liver transplantation for severe cases.[7] In this report, we describe a unique case of two consecutive children in the same family with genetically confirmed CNS type 2 who responded well to phenobarbitone without any long-term adverse effects.

Case

The proband, a 2-month-old first-born male child of a third-degree consanguineous marriage, was brought by his parents to the pediatric outpatient clinic of All India Institute of Medical Sciences in Rishikesh (India) with the chief complaint of progressive yellowish discolouration of the skin and sclera noted since day 12 of life. There was no history of high-coloured urine or pale stools after birth. Birth and perinatal history were uneventful without the presence of cephalohematoma. He had multiple hospitalisations for phototherapy, with only transient and partial improvement. There was no history of poor feeding, lethargy, seizures, blood transfusions, or bleeding tendencies. There was an absence of Rh-incompatibility between the mother and the baby (the child's blood group was A positive, and the mother's blood group was B positive).

On examination, he was alert and consolable, deeply icteric, and moderately nourished, without organomegaly or dysmorphic features. Laboratory evaluation showed: total serum bilirubin 31 mg/dL (n: 0.3–1.2 mg/dl), direct bilirubin 0.9 mg/dL (n: <1 mg/dl), hemoglobin 11.5 g/dL (n: 10.5–13.5 g/dl), WBC 8,200/uL (n: 6,000–17,000/uL), platelets 310 $\times 10^9$/L (n:150–450), reticulocyte count 1.1% (n: 0.5–1.5%), LDH 190 U/L (n:140–280 U/L). There was no evidence of haemolysis on peripheral smear. Thyroid function tests were normal. Quantitative G6PD level in blood was normal. Liver synthetic function tests, too, were within normal limits with a normal prothrombin time. Ultrasound whole abdomen depicted a normal hepato-biliary system.

The patient was started on oral phenobarbitone at 5 mg/kg/day, which gradually had to be hiked to 7 mg/kg/day, and oral calcium phosphate at 75 mg/kg/day of elemental calcium. Over 4 weeks, his indirect bilirubin fell to <10 mg/dL, with excellent clinical response in the form of marked reduction of jaundice. No side effects were noted during treatment or follow-up due to phenobarbitone. Genetic testing (whole exome sequencing, WES) confirmed a homozygous missense mutation in exon 5 of the *UGT1A1* gene (c.1456T>G; p.Y486D), classified as pathogenic. Mother was counselled for genetic counselling during the next pregnancy, which she missed.

Three years later, his younger sister presented to our centre, in week 2 of life, with progressive jaundice from day 4 of life, without high-coloured urine or acholic stools, requiring NICU admission and multiple phototherapy sessions without significant improvement. Total serum bilirubin was 16 mg/dl (n:0.3-1 mg/dl), direct bilirubin 0.7 mg/dL (n: <1 mg/dl), hemoglobin 14.1 g/dL (n: 10.5–13.5 g/dl), WBC 8,800/uL (n: 6,000–17,000/uL), platelets 270 $\times 10^9$/L (n:150–450), reticulocyte count 1.4% (n: 0.5–1.5%), LDH 234 U/L (n:140–280 U/L). Genetic analysis revealed the same pathogenic missense *UGT1A1* mutation (c.1456T>G; p.Y486D) in her as in the elder sibling. She was started on phenobarbitone alone at 5 mg/kg/day, with sustained bilirubin reduction and good growth on follow-up. Both siblings continue to remain clinically stable on phenobarbitone, without neurotoxicity or adverse drug reactions.

Discussion

Indirect hyperbilirubinemia (IH) is the most common cause of neonatal admission. Despite most newborns with IH having a good prognosis, approximately 10% of cases do not have spontaneous lowering of bilirubin levels, which may lead to severe complications, including growth retardation, encephalopathy, autism, and hearing impairment.[8] Crigler-Najjar syndrome (CNS), first described by John F. Crigler and Victor A. Najjar in 7 cases with congenital and familial non-hemolytic IH, is a rare autosomal recessive disorder due to mutations mostly in the coding regions of exons 2-5 of the uridine diphosphate glucuronosyltransferase (*UGT1A1*) gene cloned in

1991 on chromosome 2q37, leading to variable levels of UGT enzyme deficiency.[9, 10] Whereas CNS type 1 (absence of *UGT1A1* activity) infants are effectively managed only by intensive phototherapy (up to 7 hours daily) and liver transplantation, and most of them die in infancy due to kernicterus, CNS type 2 (4-10 % of residual *UGT1A1* activity) infants have a more favourable outcome.[11] They are less likely to develop bilirubin-induced neurological dysfunction (BIND), and most of them have a smooth transition to adult life.[10] The global incidence of CNS is estimated to be fewer than 1 in a million live births.[11] However, certain populations in Tunisian, Croatian, and Kuwaiti Bedouin families exhibit a higher prevalence of up to 6.1 cases per 1,000,000 live births, attributed to founder mutations.[11, 12] The clinical hallmark of CNS type 2 is persistent jaundice with risk of kernicterus during intercurrent illness. A similar benign disease called Gilbert syndrome (GS, 25-30 % of residual *UGT1A1* activity) affects 5% of the normal population and is caused by promoter region mutations in the *UGT1A1*7* gene, with a maximum serum bilirubin rising to 5 mg/dl, during periods of stress, in these children.[13]

The use of phenobarbitone in pediatric CNS type 2 has been well-documented, showing long-term safety and effectiveness. Phenobarbitone therapy is considered the gold standard of treatment in CNS type 2, inducing *UGT1A1* activity via activation of nuclear receptors such as CAR (constitutive androstane receptor) and PXR (pregnane X receptor).[7] It increases bilirubin conjugation, thereby reducing serum levels significantly. In our cases, both siblings responded well to phenobarbitone, underscoring its efficacy. Calcium phosphate in CNS type 2 acts by binding unconjugated bilirubin in the intestinal lumen, thereby reducing its enterohepatic recirculation. Though less potent alone, it can be useful as an adjunct in severe cases.[14]

Whereas CNS type 1 cases are marked by large truncating deletions or exon skipping or nonsense/stop codon mutations in the *UGT1A1* gene, CNS type 2 patients have mostly missense/point mutations in the *UGT1A1*.[10] The spectrum of *UGT1A1* variants varies greatly between different ethnicities. The compound heterozygous and homozygous G71R and Y486D variants are commonly most associated with East Asian CNS II patients from Japan and China.[15, 16] Other variants of significance include the Q357R, (TA)7, R341*, and A401P in Tunisian, Caucasian, Croatian and French populations as part of "founder effect".[10] Our report is also unique because it documents two consecutive siblings affected by CNS type 2 with the same *UGT1A1* missense pathogenic mutation, both demonstrating a robust response to *UGT1A1* induction therapy. Reports of siblings with genetically confirmed CNS type 2 are extremely limited, particularly from South Asia. Our study found the presence of a homozygous Y486D (p.Tyr486Asp) mutation, which is usually involved in the metabolism of irinotecan to its active metabolite SN-38 (7-Ethyl-10-hydroxycamptothecin), leading to irinotecan toxicity in the presence of this variant, and has not previously been reported from India.[17]

Previously, the P176L (p.Pro176Leu) has been mentioned in a 16-year-old girl from India with previous two sibling deaths in the early neonatal period. She had undergone exchange transfusions twice at day 5 and day 20 of postnatal life and did well on prolonged phenobarbitone therapy with a good neurodevelopmental outcome and normal intelligence on follow-up.[13] There have also been reports of CNS type 1, CNS type 2 and GS in the same family, albeit a different variant in the *UGT1A1* gene.[5] This explains the clinical heterogeneity of CNS in infants, with the same familial mutations having a myriad of varied presentations, probably hinting at a role of other epigenetic factors in the disease pathophysiology. Even in our case, the first sibling had a total serum bilirubin of 31 mg/dl, which is ideally seen in CNS type 1, but the behaviour of the disease process was in line with CNS type 2. Other worldwide reports of familial presence of CNS described in 20 Egyptian patients show nine siblings to have died across five families, most probably due to CNS type 1.[10] Similarly, sibling recurrence has been noted to be in five Croatian families by Kovačić et.al.[11]

Alternative therapies of severe hyperbilirubinemia in CNS type 2 include plasmapheresis and exchange transfusion, used during acute crises with dangerously high bilirubin.[7] Auxiliary partial orthotopic liver transplantation (APOLT) remains the definitive cure, though associated with lifelong immunosuppression and risks. CNS type 1 children rarely survive without APOLT. Experimental modalities, such as allogenic hepatocyte transplantation into the portal vein and AAV serotype 8-mediated gene therapy, are under evaluation, with reports suggesting their feasibility.[18-20] In our cases, phenobarbitone alone (with calcium phosphate in the elder sibling) was sufficient. If bilirubin levels had remained uncontrolled, escalation to exchange transfusion or transplantation would have been considered. The absence of adverse drug effects further reinforces phenobarbitone's safety in pediatric practice.

One of the limitations of our study was the absence of any knowledge of the long-term neuro-developmental outcome of the two cases, which will subsequently be known in follow-up. Further work-up in future should entail assessment of cognitive function and hearing in all babies with neonatal onset of CNS type 2.

Conclusion

Thus, CNS type 2 should be suspected in infants with persistent unconjugated jaundice unresponsive to phototherapy. Phenobarbitone remains the first-line therapy and is highly effective, reducing bilirubin level by up to two-thirds. Family recurrence emphasises the need for genetic confirmation, counselling, and screening. Adjuncts like calcium phosphate may aid management, while advanced therapies are reserved for non-responders. These cases add to the scarce literature on multiple affected siblings with CNS type 2 and confirm phenobarbitone's long-term safety.

Acknowledgement

The authors are grateful to the Neonatal Intensive Care Unit (NICU) team at AIIMS, Rishikesh, for being involved in the management of the second sibling in this study. The authors have asked permission from the patient's parents to write this case report and publish it in a scientific journal.

Conflict of Interest

The authors declare no conflicts of interest.

Funding Statement

This study received no external funding.

References

1. Bosma PJ. Inherited disorders of bilirubin metabolism. J Hepatol. 2003;38(1):107-17. https://doi.org/10.1016/s0168-8278(02)00359-8
2. 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. https://doi.org/10.1002/1098-1004(200010)16:4<297::Aid-humu2>3.0.Co;2-z
3. Tcaciuc E, Podurean M, Tcaciuc A. Management of crigler-najjar syndrome. Med Pharm Rep. 2021;94(Suppl No 1):S64-s7. https://doi.org/10.15386/mpr-2234
4. Kumar P, Sasmal G, Gupta S, Saxena R, Kohli S. Crigler najjar syndrome type 2 (cns type 2): An unwonted cause of jaundice in adults. J Clin Diagn Res. 2017;11(7):Od05-od6. https://doi.org/10.7860/jcdr/2017/28195.10221
5. Aarti B, Bhattacharya A, Shamima, Gupta S. Hereditary hyperbilirubinemia: An original study of four cases with review of literature. IOSR Journal of Dental and Medical Sciences. 2014;13:38-42. https://doi.org/10.9790/0853-131113842
6. Strauss KA, Ahlfors CE, Soltys K, Mazareigos GV, Young M, Bowser LE, et al. Crigler-najjar syndrome type 1: Pathophysiology, natural history, and therapeutic frontier. Hepatology. 2020;71(6):1923-39. https://doi.org/10.1002/hep.30959
7. Sambati V, Laudisio S, Motta M, Esposito S. Therapeutic options for crigler-najjar syndrome: A scoping review. Int J Mol Sci. 2024;25(20). https://doi.org/10.3390/ijms252011006
8. Lin Q, Zhu D, Chen C, Feng Y, Shen F, Wu Z. Risk factors for neonatal hyperbilirubinemia: A systematic review and meta-analysis. Transl Pediatr. 2022;11(6):1001-9. https://doi.org/10.21037/tp-22-229
9. Crigler JF, Jr., Najjar VA. Congenital familial nonhemolytic jaundice with kernicterus. Pediatrics. 1952;10(2):169-80.
10. Khedr M, Behairy B, Basiouny H, Zeitoon N, Elfert A, Zakaria H, Ammar T. Clinical and molecular study of egyptian pediatric patients with crigler-najjar syndrome. Egyptian Liver Journal. 2025;15. https://doi.org/10.1186/s43066-025-00428-w
11. Kovačić Perica M, Todorić I, Marčinković N, Džepina P, Aničić MN, Mrzljak A, Vuković J. Case report: Crigler-najjar syndrome type 1 in croatia-more than a one in a million: A case series. Front Pediatr. 2023;11:1276349. https://doi.org/10.3389/fped.2023.1276349
12. Petit FM, Bézieau S, Gajdos V, Parisot F, Scoul C, Capel L, et al. The tunisian population history through the crigler-najjar type i syndrome. Eur J Hum Genet. 2008;16(7):848-53. https://doi.org/10.1038/sj.ejhg.5201989
13. Nair KM, Lohse P, Nampoothiri S. Crigler-najjar syndrome type 2: Novel ugt1a1 mutation. Indian J Hum Genet. 2012;18(2):233-4. https://doi.org/10.4103/0971-6866.100776
14. Ghorui A, Chowdhry BK, Manjhi PK, Kumar P, Kumar CM. Evaluation of efficacy of oral calcium phosphate as an adjunct to standard-of-care regular phototherapy in cases of neonatal jaundice: A hospital-based double-blind, randomised, placebo-controlled trial. BMJ Paediatr Open. 2024;8(1). https://doi.org/10.1136/bmjpo-2024-002902
15. Takeuchi K, Kobayashi Y, Tamaki S, Ishihara T, Maruo Y, Araki J, et al. Genetic polymorphisms of bilirubin uridine diphosphate-glucuronosyltransferase gene in japanese patients with crigler-najjar syndrome or gilbert's syndrome as well as in healthy japanese subjects. J

Gastroenterol Hepatol. 2004;19(9):1023-8. https://doi.org/10.1111/j.1440-1746.2004.03370.x
16. Sun L, Li M, Zhang L, Teng X, Chen X, Zhou X, et al. Differences in ugt1a1 gene mutations and pathological liver changes between chinese patients with gilbert syndrome and crigler-najjar syndrome type ii. Medicine (Baltimore). 2017;96(45):e8620. https://doi.org/10.1097/md.0000000000008620
17. Gagné JF, Montminy V, Belanger P, Journault K, Gaucher G, Guillemette C. Common human ugt1a polymorphisms and the altered metabolism of irinotecan active metabolite 7-ethyl-10-hydroxycamptothecin (sn-38). Mol Pharmacol. 2002;62(3):608-17. https://doi.org/10.1124/mol.62.3.608
18. Yu Y, Fisher JE, Lillegard JB, Rodysill B, Amiot B, Nyberg SL. Cell therapies for liver diseases. Liver Transpl. 2012;18(1):9-21. https://doi.org/10.1002/lt.22467
19. Ambrosino G, Varotto S, Strom SC, Guariso G, Franchin E, Miotto D, et al. Isolated hepatocyte transplantation for crigler-najjar syndrome type 1. Cell Transplant. 2005;14(2-3):151-7. https://doi.org/10.3727/000000005783983250
20. D'Antiga L, Beuers U, Ronzitti G, Brunetti-Pierri N, Baumann U, Di Giorgio A, et al. Gene therapy in patients with the crigler-najjar syndrome. N Engl J Med. 2023;389(7):620-31. https://doi.org/10.1056/NEJMoa2214084