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A Rare Case of Crigler-Najjar Syndrome Type 2

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ABSTRACT

Crigler–Najjar Syndrome Type 2 (CNS2) is a rare autosomal recessive disorder characterized by unconjugated hyperbilirubinemia due to partial deficiency of the enzyme uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1). We present a case of a 13-month-old male admitted to Kanti Children's Hospital with persistent jaundice since birth. Diagnostic evaluation accompanied by gene sequencing confirmed CNS2 and the patient was effectively managed with orally administered phenobarbitone. CNS2 can be distinguished from other potential causes of unconjugated hyperbilirubinemia based on bilirubin concentration and the affected patient's response to phenobarbitone. Genetic counselling is essential for the recognition and prevention of severe hyperbilirubinemia which, in the absence of timely medical intervention, may lead to neurotoxicity.

Keywords: Case report; crigler-Najjar syndrome; genetic counseling; phenobarbitone; unconjugated hyperbilirubinemia.

INTRODUCTION

Crigler-Najjar syndrome (CNS) is a rare genetic disorder affecting approximately fewer than 1 in 1 million newborns.[1] Mutations in the UGT1A1 gene encoding uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1) results in reduced or absent conjugation of bilirubin. CNS is classified into two types. Type 1 (CNS1) is defined by a total absence of UGT1A1 enzyme activity, unresponsive to phenobarbitone, fatal without liver transplantation. The more benign form, Type 2 (CNS2) is caused by a single base pair mutation leading to decreased enzyme activity and responds well to phenobarbitone. CNS2 leads to chronic, mild to moderate unconjugated hyperbilirubinemia and icterus, typically diagnosed in infancy or early childhood.[2,3] This case report showcases a rare presentation of Crigler-Najjar Syndrome Type 2, providing insights into its diagnosis via genetic testing and effective management with phenobarbitone. It highlights the critical role of genetic counseling in avoiding neurotoxicity.

CASE PRESENTATION

A 13-month-old male from Province 5, Nepal, presented with persistent jaundice since birth, visible on the sclera and gradually spreading downward his entire body. His birth was full-term, with a normal APGAR score and no significant postnatal complications. Jaundice remained despite home sunlight exposure. There was no dark urine, clay-colored stools, or pruritus, ruling out liver dysfunction as a cause for jaundice. The child's growth and development were otherwise normal.

Initial assessment revealed he was hemodynamically stable with severe icterus extending up to the level of upper thighs, but no abdominal abnormalities. Relevant investigations were ordered and hemolytic causes were excluded due to his normal reticulocyte. The 13-month-old patient exhibited elevated total bilirubin (12.26 mg/dl) and slightly raised liver enzymes (AST 112 U/L, ALT 91 U/L, ALP 449 U/L), indicating unconjugated hyperbilirubinemia. Whole exome sequencing confirmed Crigler-Najjar Syndrome Type 2 with a heterozygous missense variant in the UGT1A1 gene, (chr2: g.2337724113T>G; Depth: 148x) causing substitution of the amino acid Aspartic acid for Tyrosine at codon 486.

Oral phenobarbitone was then started at 4 mg/kg/day. Within the next three days, the child's total serum bilirubin dropped significantly to 6.3 mg/dl, confirming CNS2. By the end of the next two weeks, the bilirubin

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levels gradually decreased to 2.9 mg/dl. The child remained clinically stable with only a single episode of mild fever. Parents were provided with adequate genetic counselling and advised to continue phenobarbitone and schedule a follow-up in a month.

DISCUSSION

The elevated bilirubin concentrations seen in neonatal jaundice, can stem from various underlying conditions. Of these, an uncommon but significant cause is Crigler-Najjar Syndrome (CNS), manifesting as unconjugated hyperbilirubinemia. A differential diagnosis of CNS should be considered in neonates with persistent jaundice sans evidence of hemolysis or liver disease.[4] However, confirmatory diagnosis requires identification of the mutation via gene sequencing, although this may not be an available option in resource-poor settings.[2]

CNS itself is differentiated into two types: CNS1 and CNS2. CNS1 is associated with relatively higher bilirubin levels, typically ranging between 20 and 40 mg/dL, owing to a complete absence of UDP-glucuronosyltransferase (UGT) enzyme activity, which is vital for bilirubin conjugation. In contrast, CNS2 features lower bilirubin levels (generally below 20 mg/dL) and UGT activity. This residual activity allows CNS2 patients to respond to treatment with phenobarbitone, unlike CNS1 patients.[5]

The barbiturate, phenobarbitone, can substantially reduce serum bilirubin levels in CNS2 by inducing UGT1A1 enzyme expression, thus augmenting bilirubin conjugation. Its efficacy in the treatment of CNS2 patients has been verified, as it displays a significant reduction in bilirubin levels. This is in contrast to CNS1 patients, who do not respond to phenobarbitone treatment due to the absolute lack of UGT enzyme activity. Thus, the patient's response to phenobarbitone can help discriminate between CNS types and guide treatment strategies.[5]

Likewise, a study published in 2015 by Sinha R et al. assessed the impact of phenobarbitone on bilirubin levels in children with isolated unconjugated hyperbilirubinemia. In the study, it was found that among 20 children, 12 displayed normalized bilirubin levels (suggesting Gilbert syndrome), while in the remaining a 30-40% reduction in bilirubin was observed, indicative of CNS2.[6] In CNS2 patients, treatment involves administering phenobarbitone at doses of 3-5 mg/kg/day, up to a maximum of 60-180 mg/day, either in a single or divided dose. For pregnant women, the dosage is adjusted to 30-60 mg/day to mitigate potential teratogenic effects.[7]

However, genetic counseling plays just as crucial a role in the management of CNS2. To begin with, it is important for parents to recognize that CNS2 is a chronic condition requiring lifelong pharmacological intervention, unlike physiological jaundice which resolves on its own. Families should be informed about the potential for inheritance, and factors that may exacerbate hyperbilirubinemia, such as infections, stress, fasting, and certain medications that displace unconjugated bilirubin from plasma protein binding sites; namely: sulfonamides, salicylates and penicillin. Effective genetic counseling helps the patient party in managing their expectations and promoting adherence to the treatment regimen.[5]

While pediatricians or neonatologists manage the basic clinical aspects of the condition, a multidisciplinary approach can optimize patient care. Genetic counselors can provide insights regarding genetic implications and inheritance patterns. Neurologists can address any related neurological issues, whereas nutritionists may offer dietary advice to prevent excessive bilirubin accumulation while maintaining sufficient nutrition.[8]

In the case discussed, the clinical findings were observed over a 17-day period, limiting the assessment of long-term treatment efficacy and overall patient progress. Extended follow-up is required to fully analyze the effectiveness of treatment, potential side effects and monitor patient outcomes. This emphasizes the need for additional research with longer follow-up durations to gain a better understanding of the long-term management and prognosis of CNS2.

CONCLUSIONS

CNS2 has a better prognosis than CNS1 and is responsive to oral phenobarbitone. Although usually not associated with kernicterus, lifelong treatment with phenobarbitone is a must, to avoid neurotoxicity associated with severe hyperbilirubinemia. Genetic counseling informs the patient party not only of inheritance patterns, but of the necessity to promptly seek medical management for severe jaundice precipitated by various factors. Hence, the use of phenobarbitone in conjunction with genetic counseling is key to ensuring effective therapy. In order to analyze treatment efficacy and patient progress, there is a need for further research with a relatively longer follow-up period.

CONFLICT OF INTEREST:

None

REFERENCES

1. Abdul Raffay E, Liaqat A, Khan M, Awan AI, Mand B. A Rare Case Report of Crigler Najjar Syndrome Type II. Cureus. 2021 Jan 12;13(1):e12669. https://www.ncbi.nlm.nih.gov › articles › PMC7880822

2. He T, Geng X, Zhu L, Lin X, Wang L. Type II Crigler-Najjar syndrome: a case report and literature review. Frontiers in Medicine. 2024 May 9;11:1354514. https://www.ncbi.nlm.nih.gov › articles › PMC11112071

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. Clinical Case Reports. 2023 Nov;11(11) [PubMed]

4. Peters AL, Balistreri WF. Metabolic diseases of the liver: Inherited Deficient Conjugation of Bilirubin (Familial Nonhemolytic Unconjugated Hyperbilirubinemia). In: Kliegman RM, St. Geme JW, Blum NJ, Tasker RC, Shah SS, Wilson KM, editors. Nelson textbook of pediatrics. 21st edition. Philadelphia, MO: Elsevier; 2019. p. 2101-3.

5. Liaqat A, Shahid A, Attiq H, Ameer A, Imran M. Crigler-Najjar Syndrome Type II Diagnosed in a Patient with Jaundice Since Birth. J Coll Physicians Surg Pak. 2018 Oct;28(10):806-808.[PubMed]

6. Sinha R, Dalal S, Sodhi K. Diff erentiating Gilbert Syndrome from Crigler Najjar Syndrome Type 2 by Phenobarbitone Test. J Nepal Paediatr Soc. 2015;35(1):82-84.[Article]

7. 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 Jul;11(7):OD05-OD06.[PubMed]

8. Bhandari J, Thada PK, Yadav D. Crigler Najjar Syndrome [Internet]. PubMed. Treasure Island (FL): StatPearls Publishing; 2020. https://www.ncbi.nlm.nih.gov/books/NBK562171/