

Recurrent Neonatal Hyperbilirubinemia Revealing Combined Crigler-Najjar and Gilbert Syndromes: A Case Report

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Abstract

Severe or recurrent neonatal jaundice warrants evaluation for underlying genetic disorders of bilirubin metabolism, particularly after excluding hemolysis and infection. We report the case of a term newborn with marked unconjugated hyperbilirubinemia requiring repeated hospitalizations and multiple courses of phototherapy. Molecular genetic testing revealed the coexistence of Crigler-Najjar syndrome and Gilbert syndrome, providing a genetic explanation for the severity and persistence of jaundice. This case highlights difficulties of its management and the importance of comprehensive genetic analysis in neonates with unexplained hyperbilirubinemia, especially in consanguineous families.

Keywords: Crigler-Najjar syndrome; Gilbert syndrome; Neonatal hyperbilirubinemia; Combined mutation; Case report

Introduction

Crigler-Najjar syndrome (CNS) and Gilbert syndrome (GS) are inherited disorders of bilirubin conjugation caused by pathogenic variants in the UGT1A1 gene, which encodes the enzyme uridine diphosphate–glucuronosyltransferase 1A1 (UGT1A1) [2,4,6]. These conditions represent a spectrum of disease severity correlating with residual UGT1A1 enzymatic activity [2,4].

CNS lies at the severe end of the spectrum, whereas GS is the most common and typically mildest form [2,5,8]. CNS type 1 is characterized by complete or near-complete absence of UGT1A1 activity, often due to homozygous pathogenic variants in the coding region [2,6]. In contrast, GS is an autosomal recessive condition most commonly associated with a homozygous A(TA)₇ insertion in the promoter region (UGT1A1*28 allele), resulting in partial enzyme deficiency [1,5].

The coexistence of a homozygous pathogenic coding-region mutation and a homozygous promoter-region variant is rarely reported [2,6]. This combination can lead to compounded reduction in UGT1A1 activity, resulting in a phenotype more severe than isolated GS and more complex than classic CNS [2,4,6]. Therefore, comprehensive molecular characterization is essential to interpret the clinical presentation and guide management [2,4].

Case Presentation

A term newborn was admitted on day 3 of life for severe jaundice. The infant was born at 41 weeks of gestation to consanguineous parents with no family history of anemia or blood transfusions. The mother, a 29-year-old primigravida with AB Rh-negative blood group, had an uncomplicated pregnancy and delivery. The newborn showed good initial adaptation.

Total serum bilirubin levels were markedly elevated: 280 $\mu\text{mol/L}$ on day 3, 374 $\mu\text{mol/L}$ on day 5, and peaking at 390 $\mu\text{mol/L}$ on day 7. The infant required prolonged hospitalization for 11 days with phototherapy. Rh incompatibility was initially suspected, but direct Coombs test was negative with no evidence of hemolysis.

The infant was readmitted on day 11 with recurrent jaundice (bilirubin 278 $\mu\text{mol/L}$). Investigations ruled out endocrine and infectious causes: thyroid function tests, serum cortisol, C-reactive protein, and urine culture were normal.

Given the severity and recurrence of unconjugated hyperbilirubinemia, molecular genetic testing was performed. Results revealed a homozygous pathogenic mutation c.1070A>G in the coding region of UGT1A1, along with a homozygous A(TA)₇ insertion in the promoter region, confirming combined Crigler-Najjar syndrome and Gilbert syndrome.

The baby had 3 phototherapy sessions per week at the hospital sessions; lasting six hours spread throughout the day, until the age of 2 months. Home-based phototherapy combined with phenobarbital (5mg/kg/day) were started immediately upon diagnosis.

The infant is now 18 months old and has good psychomotor development (walks independently and responds to his parents with two-syllable words). The parents have not noticed any abnormal movements. The bilirubin levels decrease between [150-250 $\mu\text{mol/L}$] But parents complain about difficulties during home phototherapy sessions.

Discussion

Severe recurrent unconjugated hyperbilirubinemia in neonates necessitates thorough etiological evaluation after excluding common causes such as hemolysis, infection, and endocrine disorders [3,7]. In our patient, early onset, marked bilirubin elevation, poor sustained response to phototherapy, and recurrence after discharge suggested an underlying disorder of bilirubin conjugation [2,4].

CNS and GS represent a continuum of inherited defects in bilirubin glucuronidation due to UGT1A1 variants [2,4,6]. The clinical phenotype correlates with residual UGT1A1 activity [2,4]. CNS type 1 typically presents with severe neonatal jaundice poorly responsive to phototherapy [3,6], whereas GS usually manifests later in life with mild intermittent hyperbilirubinemia [5,8].

Our case is notable for the coexistence of a homozygous pathogenic coding-region mutation (c.1070A>G) and a homozygous promoter-region A(TA)₇ variant, a rarely reported combination [2,6]. This dual genetic defect likely resulted in compounded UGT1A1 deficiency, explaining the severe and recurrent neonatal presentation [2,4,6]. Consanguinity likely contributed to the homozygous state of both variants [2,6].

Homozygosity for a coding region mutation (CNS) combined with homozygosity for the promoter mutation (GS) leads to a significant reduction in UGT1A1 enzyme activity, presenting in the neonatal period. The specific mutation (c.1070A>G vs. c.164A>G) and its location in the gene may account for the differing severity and treatment requirements (combination therapy vs. phenobarbitone alone) [9].

Therapeutically, the infant was managed with intensive and home-based phototherapy, combined with phenobarbital. Phenobarbital is known to induce residual UGT1A1 activity in patients with preserved enzymatic function [3,6]. The partial clinical response observed supports the presence of residual enzyme activity despite severe presentation [2,4,6].

The bilirubin levels are maintained in the 150-250 $\mu\text{mol/L}$ range (~ 8.8 -14.6 mg/dL), which is higher than Rangan and al's case after 16 months of home-based phototherapy and phenobarbitone. The case of Rangan and al. was managed with daily oral phenobarbitone from diagnosis until a trial of withdrawal at 5.5 years with bilirubin level (2.6 mg/dL on therapy) [9]. This suggests that our case have a more severe enzyme deficiency or that the combination therapy is necessary to keep levels safe more than phenobarbitone alone.

At 18months, our case has a good neurological outcome also Rangan and al's case who keep a normal development with no signs of bilirubin induced neurotoxicity until the age of 5.5years [9]. But, parents felt stressed and overwhelmed with home phototherapy and they faced difficulty to keep their infant. Consequently, the duration and the number of phototherapy sessions are reduced to a maximum of 2 or 3 hours a day because the infant becomes agitated and refuse it. Despite this, the bilirubin level still the same. The problem of this case is long-term management and weaning. The Rangan and al case attempted weaning off phenobarbitone at 5.5 years [9]. The question of weaning is still years away for this case. The decision will depend on whether the bilirubin levels can be maintained at a safe level ($< \sim 170$ -200 $\mu\text{mol/L}$ or < 10 mg/dL in an older child, though exact thresholds are debated) without phototherapy, and only on phenobarbitone.

Molecular genetic testing was decisive in establishing the diagnosis and clarifying pathophysiology [2,4]. Early genetic characterization is crucial for accurate diagnosis, prognosis, therapeutic planning, and genetic counseling [2,6]. Identification of combined UGT1A1 defects may influence long-term management, including prolonged phototherapy and neurological surveillance [3,4].

This case expands the clinical spectrum of UGT1A1 mutations and underscores the potential severity of combined promoter and coding-region variants. Comprehensive molecular analysis should be considered in neonates with severe or recurrent unconjugated hyperbilirubinemia, especially in consanguineous families [2,4,6].

And, it strongly supports the necessity of genetic counseling: the confirmed homozygous mutations mean there is a 25% recurrence risk for any future pregnancy. Prenatal diagnosis (amniocentesis/CVS) or preimplantation genetic diagnosis would be options to discuss.

Conclusion

This case highlights the importance of considering inherited disorders of bilirubin conjugation in neonates with severe or recurrent unconjugated hyperbilirubinemia after excluding common etiologies. Coexistence of homozygous pathogenic variants in both coding and promoter regions of UGT1A1 can result in compounded enzymatic deficiency and an atypically severe neonatal phenotype [2,4,6].

Early molecular genetic testing is essential for accurate diagnosis, therapeutic guidance, and genetic counseling, particularly in consanguineous contexts [2,6]. Combined management with phototherapy and enzyme-inducing agents like phenobarbital may offer partial benefit in cases with residual UGT1A1 activity [3,6].

This report expands the phenotypic spectrum associated with UGT1A1 mutations and emphasizes the need for individualized diagnostic and therapeutic strategies in neonates with complex genetic hyperbilirubinemia [2,4].

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