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Case Report

Recurrent severe hyperbilirubinemia due to compound heterozygous UGT1A1 mutations: an early neonatal presentation of Gilbert syndrome

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ABSTRACT

Gilbert syndrome, a relatively common but less conspicuous condition, is characterized by intermittent episodes of mild to moderate unconjugated hyperbilirubinemia due to limited activity of the enzyme UGT1A1. It is usually benign and often remains unnoticed due to overlap with physiological jaundice. We report a case of term male neonate who developed four distinct episodes of severe, recurrent unconjugated hyperbilirubinemia within the first month of life, each requiring intensive phototherapy. Extensive evaluation excluded hemolysis, sepsis, endocrine dysfunction, and cholestatic liver disease as cause of jaundice. Given the atypical presentation with recurrent neonatal jaundice and no identifiable underlying cause, genetic testing was performed, which revealed compound heterozygosity for UGT1A1 variants (-3279T>G promoter polymorphism and 211G>A exon 1 mutation), confirming Gilbert syndrome. The infant responded promptly to phototherapy and had normal BERA and MRI brain with age-appropriate developmental milestones. This case highlights an atypically severe and recurrent neonatal presentation of Gilbert syndrome in the absence of known exacerbating factors and emphasizes the importance of genetic testing to distinguish Gilbert syndrome from Crigler-Najjar syndrome, guide management, and avoid unnecessary invasive interventions.

Keywords: Neonatal jaundice, Gilbert syndrome, Phototherapy, Hyperbilirubinemia, UGT1A1

INTRODUCTION

Gilbert's syndrome is chronic, non-hemolytic unconjugated hyperbilirubinemia caused due to reduced activity of the enzyme uridine diphosphate-glucuronosyltransferase (UGT).[1] Various mutations of the UGT1A1 gene have been detected in promoter or coding regions of patients which have been associated with Gilbert syndrome, Criggler Najjar syndrome type II and type I, in increasing order of their severity.[2,3] Gilbert syndrome, the mildest form of UGT1A1 reduced activity, manifests with fluctuating serum bilirubin levels, and can be often exacerbated by stress, fasting, or infections.[4] The hereditary nature of Gilbert syndrome, caused by mutations in the UGT1A1 gene, underscores its relevance in clinical genetics and neonatal care. While Gilbert syndrome is predominantly asymptomatic and does not typically require treatment, it may occasionally lead to exaggerated neonatal jaundice or prolonged episodes of mild jaundice.[7,8]

Although Gilbert syndrome typically presents later in childhood or adolescence with mild hyperbilirubinemia, early neonatal presentation with recurrent, severe jaundice episodes requiring multiple courses of intensive phototherapy is uncommon, particularly in the absence of hemolysis, prematurity, or enzymatic deficiencies. Compound heterozygous UGT1A1 mutations contributing to such a phenotype have been rarely described in neonates, making this case clinically significant.

CASE REPORT

A term baby boy, born out of non-consanguineous parents in third order, with mother blood group AB positive was delivered at our centre. The baby was born at 38 weeks of gestational age through emergency lower segment cessarean section and had AB negative blood group. The baby had adequate weight, length and head circumference according to WHO growth chart. Routine bilirubin screening at 48 hours of life was found to be normal. The baby presented with severe hyperbilirubinemia on Day 4 of life with serum bilirubin levels reaching upto 21.3 mg/dL. Intensive phototherapy was administered for 36 hours and bilirubin levels decreased to 11.5 mg/dL, following which the baby was discharged. The baby was again readmitted on day 21 of life with serum bilirubin levels reaching upto 26.5 mg/dL. Intensive phototherapy was administered for 36 hours and subsequently, bilirubin levels normalised to 13.8 mg/dL.

The baby witnessed recurrences of hyperbilirubinemia on day 23 and day 31 of life with serum bilirubin levels reaching upto 18 mg/dL and 18.3 mg/dL respectively, which were again treated with intensive phototherapy for 24 hours. All episodes responded well to the phototherapy.

There was no evidence of encephalopathy (BIND: 0/9) nor any dysmorphic features were noted. Further, the baby was feeding well and growing well. No significant family history of medical issues.[9] Urine and stool color were also normal. There were no clinical features suggesting of concealed haemorrage, splenomegaly and hepatomegaly. Overt hemolytic hyperbilirubinemia was excluded on the basis of normal hemoglobin values, reticulocyte counts, direct Coombs' Test and the results of peripheral blood smear and G6PD level.[5,6] Further, albumin level, direct bilirubin levels and TFT levels were also found to be normal. In view of recurrent jaundice needing phototherapy corroborated with no other underlying cause, genetic testing was performed. Genomic DNA was isolated from lymphocytes, and the exons and the promoter regions of the UGT1A1 gene were amplified using polymerase chain reaction. Mutation analysis of the UGT1A1 gene revealed that the patient had compound heterozygosity for two different polymorphisms in the promoter region (-3279T>G) and in exon 1 (211G>A).[3,7]

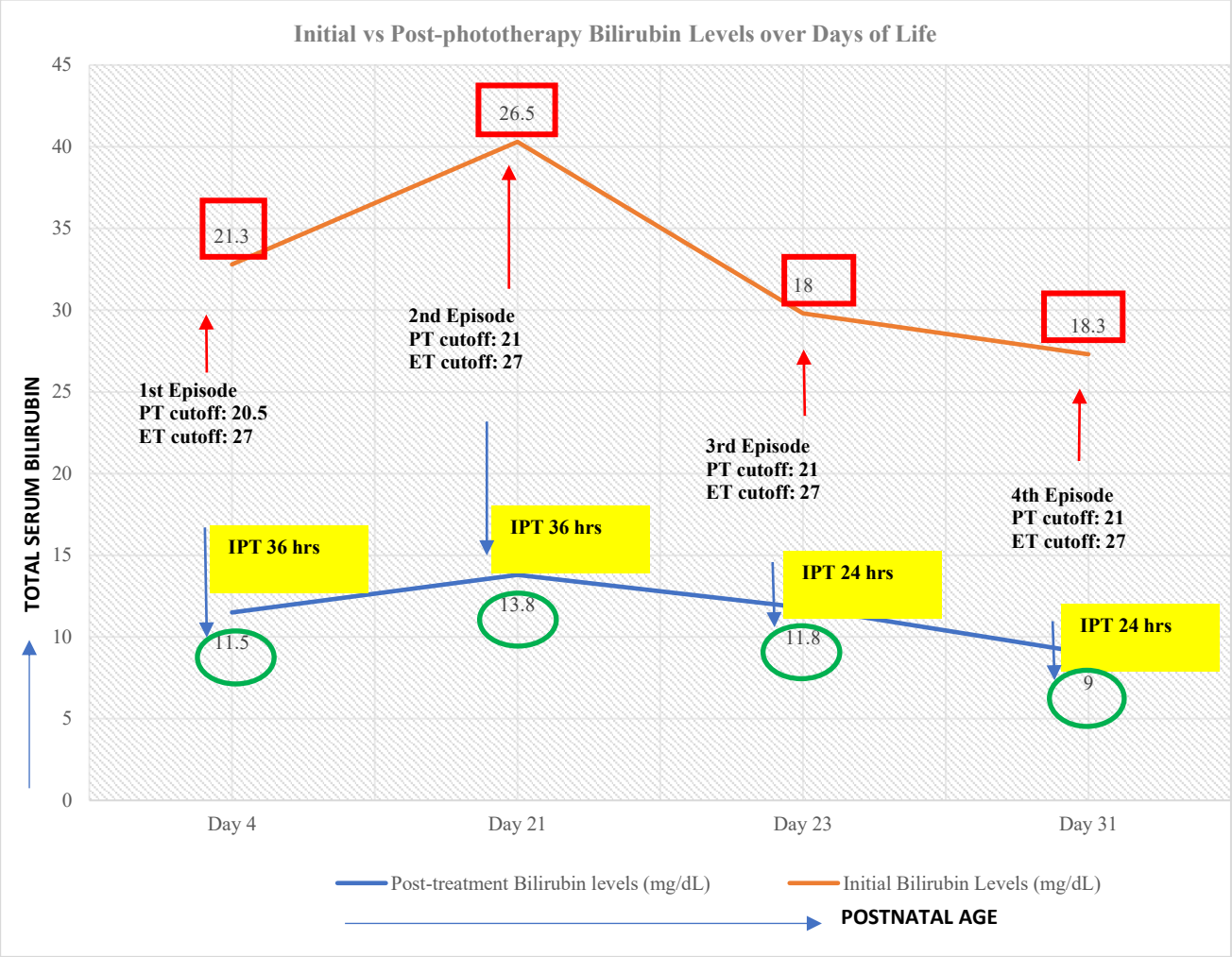

Figure 1: Depiction of 4 consecutive episodes of neonatal jaundice.

DISCUSSION

The present case illustrates an unusual neonatal presentation of Gilbert syndrome characterized by early onset, recurrent, and phototherapy-dependent unconjugated hyperbilirubinemia, occurring without identifiable precipitating factors such as hemolysis, G6PD deficiency, infection, or prematurity. This pattern differs from the more typical mild, self-limited neonatal jaundice or later childhood presentation commonly described in Gilbert syndrome.

A review of previous studies (Table 1) highlights that while most reported cases of neonatal Gilbert syndrome presented with mild jaundice or single phototherapy-responsive episodes, our case exhibited four distinct episodes of severe hyperbilirubinemia, requiring intensive phototherapy on each occasion. Compared to Nguyen et al Maruo et al and Rathi et al where jaundice was resolved with episodic phototherapy or minimal interventions, our patient required multiple hospital admissions despite having no signs of hemolysis, hepatic dysfunction, or sepsis.[12-14]

The genetic findings in our case further distinguish it from previous reports. While studies such as Sun et al identified a single homozygous UGT1A1 mutation (P364L), and Tiwari et al reported that the promoter polymorphisms like -3297 G>T and (TA)6>(TA)7, our patient demonstrated compound heterozygosity for two distinct UGT1A1 variants (-3279T>G and 211G>A).[17,18] This mutation pattern with presence of compound heterozygosity and involving both promoter and coding region variants has been rarely reported in neonates and may account for the severity and recurrence observed in this infant. While individual UGT1A1 polymorphisms are commonly associated with mild hyperbilirubinemia, the combined effect of multiple variants may result in clinically significant bilirubin accumulation during the neonatal period, when hepatic conjugation capacity is physiologically limited.

Recurrent severe neonatal jaundice should prompt further investigation beyond routine causes like hemolysis, sepsis, and hepatic dysfunction. Gilbert syndrome can present with atypical severity in neonates, especially in cases with compound heterozygous UGT1A1 mutations. Genetic testing is essential in cases of unexplained, recurrent hyperbilirubinemia to differentiate Gilbert syndrome from Crigler-Najjar syndrome.

Phototherapy remains the mainstay of treatment, but persistent episodes may require long-term monitoring and individualized management. Early diagnosis of genetic hyperbilirubinemia can guide future prenatal counselling and prevent unnecessary interventions in subsequent pregnancies.

Table 1: Clinical profile of infants diagnosed with Gilbert syndrome: a review of literature.

Authors	Year	Age of onset	Presentation	Diagnostic methods	Genetic findings	Management	Outcome
Nguyen et al[12]	2020	2 weeks	Unexplained jaundice with no hemolysis	Bilirubin profile, genetic screening	UGT1A1 polymorphism	Phototherapy, lifestyle advice	Improved without further interventions
Maruo et al[13]	2000	Neonatal	Prolonged unconjugated hyper bilirubinemia	Serum bilirubin, genetic testing	UGT1A1 mutations	Phototherapy, monitoring	Resolution of jaundice
Rathi et al[14]	2010	Neonatal	Unconjugated hyperbilirubinemia	Genetic testing	UGT1A1 polymorphisms	Supportive care	Resolved with observation
Ismail et al[15]	2011	Neonatal	Severe hyper-bilirubinemia resistant to phototherapy	Serum bilirubin, family history, genetic analysis	UGT1A1 polymorphism	Phenobarbital therapy	Reduction in bilirubin levels
Kaplan et al[16]	2001	Neonatal	Severe hyper bilirubinemia with G6PD deficiency	Serum bilirubin, G6PD screening genetic testing	G6PD deficiency, UGT1A1 mutation	Phototherapy, exchange transfusion	Resolved jaundice with treatment
Sun et al[17]	2017	Neonatal	Severe unconjugated hyperbilirubinemia	Serum bilirubin, genetic analysis	UGT1A1 P364L homozygosity	Phototherapy, possible liver transplantation	Variable; some required transplantation
Tiwari et al[18]	2014	Neonatal	Neonatal hyperbilirubinemia	PCR, SSCP, sequencing	UGT1A1 variants incl. -3297 G>T, (TA)6>(TA) 7	Phototherapy, monitoring	Identified gene-environment risk interaction
Agrawal et al[19]	2009	Neonatal	Unconjugated hyperbilirubinemia	Serum bilirubin, PCR-SSCP, PCR-RFLP, genetic testing	(TA)n promoter polymorphism detected in 89.6% of cases; novel Ala72Pro mutation; no Gly71Arg mutation found	Phototherapy, monitoring	Jaundice resolved; genetic risk factors identified

*Studies involving coexisting hemolytic disorders or older age groups are included for comparison.

CONCLUSION

This case underscores that even though Gilbert syndrome is benign, it can present in neonates with recurrent severe hyperbilirubinemia requiring repeated phototherapy, particularly in the setting of compound UGT1A1 mutations. Such repeated severe presentations should prompt further genetic evaluation to distinguish Gilbert syndrome from Crigler-Najjar syndrome, which carries a higher risk of kernicterus and requires more aggressive interventions. The findings emphasize the importance of individualized neonatal jaundice management, considering genetic predisposition, bilirubin kinetics, and response to treatment to optimize long-term outcomes.

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