

# Case of Severe Unconjugated Hyperbilirubinemia in a Neonate Heterozygous for Gilbert Syndrome

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## Abstract

We present an unusual case of unconjugated hyperbilirubinemia in a 6 day old infant. The bilirubin peaked at 20.1/0.6 mg/dL. A work-up for a hemolytic process or metabolic disorder was negative. Crigler-Najjar was suspected. Phenobarbital was given for 3 days with no change in bilirubin level. He was discharged home after 20 days of phototherapy with a bilirubin of 3.1/0.4 mg/dL. Five months later, his bilirubin was 0.2 mg/dL. His genetic testing came back positive for a heterozygous mutation for Gilbert Syndrome. In the UGT1A1 gene he had the following mutations: heterozygous \*28 (TA 6/7) (c. 40-39insTA), heterozygous \*60 (c-3275T>G), and heterozygous \*93 (c.-3152G>A). This result is consistent with a carrier state for unconjugated hyperbilirubinemia and may be associated with mild to moderate hyperbilirubinemia. The relevance of this haplotype of polymorphisms to hyperbilirubinemia in the neonate has not been established. Gilbert syndrome is the most common hereditary cause of increased bilirubin but is typically associated with mild hyperbilirubinemia, around 3 mg/dL. In the homozygous state, diminished bilirubin glucuronidation is observed but it is questionable if the same amount of decreased activity can be seen in the heterozygous state. It has been proposed that when additional mutations exist in conjunction with a heterozygous state, neonatal hyperbilirubinemia is more pronounced. We believe that unexplained unconjugated hyperbilirubinemia should raise the suspicion of a UGT1A1 gene mutation and should prompt genetic testing. Gilbert syndrome should be added to the differential of severe unconjugated hyperbilirubinemia in the neonate.

## Introduction

Jaundice is not an uncommon entity in the newborn and is encountered frequently by pediatricians. The differential diagnosis for indirect hyperbilirubinemia can be vast, making it imperative for the pediatrician to have an understanding of the different etiologies of increased bilirubin levels. Unconjugated hyperbilirubinemia can be caused by bilirubin overproduction (i.e. hemolysis), impaired hepatic bilirubin uptake (i.e. reduced hepatic blood flow or certain drugs), or impaired hepatic bilirubin conjugation (i.e. Gilbert syndrome and Crigler-Najjar syndrome Types I and II). If unconjugated hyperbilirubinemia is left untreated, it can have neurotoxic effects on the neonate with lifelong repercussions. Here we discuss a case of neonatal unconjugated hyperbilirubinemia with an unexpected diagnosis of Gilbert syndrome.

## Patient Presentation

A six day old term infant presented with unconjugated hyperbilirubinemia. He had received phototherapy for two days while in the newborn nursery for a bilirubin of 14.5/0.4 mg/dL and was discharged home. Discharge bilirubin was 11.5 mg/dL. Bilirubin levels were followed daily. On day of life six his bilirubin was 19.4/0.6 mg/dL, at which time he was admitted for phototherapy. Upon admission his vital signs were stable, he was in no distress, and was visibly jaundiced to the level of the torso. He had been feeding every three hours either breast milk or formula. His stools were yellow in color. Total bilirubin peaked the next day at 20.1 mg/dL with a direct bilirubin of 0.6. His hemoglobin was 16.1 g/dL at time of admission and dropped to 6.1, 10 days later. He was transfused 15 cc/kg of packed red blood cells. Post-transfusion hemoglobin was 9.2 g/dL. Seven days later, his hemoglobin dropped again to 6.9 and he was transfused an additional 15 cc/kg of packed red blood cells. Throughout this period, he clinically remained stable. Reticulocyte count peaked at 9.9 and a peripheral smear demonstrated schistocytes and bite cells, suggesting a hemolytic process. However, Coomb's test, haptoglobin, and G6PD screening were all within normal limits, essentially ruling out a hemolytic process. Ultrasounds of his abdomen and head were performed to look for a source of bleeding, and were both normal. Screening for metabolic

disorders including plasma amino acids and urine organic acids was unremarkable. Crigler-Najjar was suspected. A trial of Phenobarbital was given for 3 days with no significant change in his bilirubin level. His hemoglobin remained stable and his bilirubin eventually decreased to 3.1/0.4 mg/dL after 20 days of phototherapy. He was discharged home. Five months later, his total bilirubin remains normal at 0.2 mg/dL.

Several weeks after discharge, his genetic testing came back positive for a heterozygous mutation for Gilbert Syndrome, with an additional thymine and adenine (TA) base pair. In the UGT1A1 gene he had the following mutations: heterozygous \*28 (TA 6/7) (c. 40-39insTA), heterozygous \*60 (c-3275T>G), and heterozygous \*93 (c.-3152G>A). This result is consistent with a carrier state for unconjugated hyperbilirubinemia and may be associated with mild to moderate hyperbilirubinemia. This promoter TA7 repeat polymorphism when linked with these two addition alterations, (c-3275TG and c-3152GA), results in decreased glucuronidation capacity [1]. The \*60 allele is associated with reduced transcription of UGT1A1 and reduced activity of the UGT1A1 enzyme in adult patients. [2,3] The relevance of this haplotype of polymorphisms to hyperbilirubinemia in the neonate has not been established.

## Discussion

When looking at hereditary hyperbilirubinemia, those that result in primary unconjugated hyperbilirubinemia are Gilbert syndrome, Crigler-Najjar syndrome Type I and Crigler-Najjar syndrome Type II.

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Crigler-Najjar syndromes were our primary considerations as Gilbert syndrome usually causes mild hyperbilirubinemia, with bilirubin levels typically around 3 mg/dL [4].

Gilbert syndrome, found in 3% to 10% of the population, is the most common hereditary cause of increased bilirubin and is an autosomal recessive condition that is characterized by intermittent jaundice in the absence of hemolysis or underlying liver disease but generally does not present until after puberty.

Gilbert syndrome may be precipitated by dehydration, fasting, menstrual periods, or stress, such as inter current illness or vigorous exercise.

A breakthrough in understanding the genetic basis of Gilbert syndrome was achieved in 1995, when abnormalities in the TATAA region of the promoter were identified. The addition of 2 extra bases (TA) to the TATAA region interferes with binding of the transcription factor IID and results in reduced expression of the bilirubin-UGT1 enzyme. In the homozygous state, diminished bilirubin glucuronidation is observed but it is questionable if the same amount of decreased activity can be seen in the heterozygous state. In the Western world, 9% of the population is homozygous and 30% are heterozygous for the variant promoter TA 6/7. A study by *Fernandez et al.* demonstrated that approximately 50% of the adult Spanish population is heterozygous for the 6/7 genotype. *Ulgentalp et al.* looked at 110 Turkish infants and found 46% of them to be heterozygous for the 6/7 genotype. These two studies have suggested that the heterozygous TA 6/7 mutation does not significantly contribute to unexplained pathologic or prolonged hyperbilirubinemia. However, a study by *Bancroft et al.* [5] proposed that the homozygous TA 7/7 polymorphism is associated with a more rapid rise in jaundice over the first 2 days of life when compared to other newborns.

Our patient is interesting in that his bilirubin did not peak until day 6 of life, but this could be due to the heterozygous polymorphism causing a mild to moderate decrease in enzyme activity. Additional mutations were also found also in our patient. It is believed that when these mutations exist in conjunction with a heterozygous state, neonatal hyperbilirubinemia is more pronounced [5].

Gilbert syndrome can also frequently coexist with other conditions associated with unconjugated hyperbilirubinemia, such as hereditary hemolytic anemia, making the degree of neonatal jaundice more severe. However, this was not observed in our patient. The etiology of the severe anemia in our patient continues to be unclear and is not typically associated with defects in the UGT1A1 gene.

Phenobarbital and other enzyme inducers of the bilirubin-UGT1 system will normalize plasma bilirubin in patients with Gilbert syndrome. This is predominantly due to accelerated bilirubin clearance from enzyme induction but is also due to reduced bilirubin turnover. Steroids can also reduce plasma bilirubin levels in Gilbert syndrome by increasing hepatic uptake and storage of bilirubin. Phenobarbital can be used to differentiate between Crigler-Najjar Type I and Type II, as Type II will respond with a decrease in indirect bilirubin levels. Phenobarbital was used in our patient, but no response was seen, possibly due to the short duration of treatment.

We believe that unexplained moderate to severe prolonged indirect hyperbilirubinemia should raise the suspicion of a UGT1A1 gene mutation. This should prompt genetic testing to help differentiate between Crigler-Najjar and Gilbert's disease as their clinical courses and treatment vary significantly. There is conflicting data as to whether the heterozygous state of Gilbert syndrome can cause severe neonatal

unconjugated hyperbilirubinemia in the absence of other disease. Our case supports those both homozygous and heterozygous forms of Gilbert syndrome should be added to the differential of severe prolonged unconjugated hyperbilirubinemia in the neonate.

## References

1. Innocenti F, Grimsley C, Das S, Ramirez J, Cheng C, et al. (2002) Haplotype structure of the UDP-glucuronosyltransferase 1A1 promoter in different ethnic groups. *Pharmacogenetics* 12: 725-733.
2. Sugatani J, Yamakawa K, Yoshinari K, Machida T, Takagi H, et al. (2002) of a defect in the UGT1A1 gene promoter and its association with hyperbilirubinemia. *Biochem Biophys Res Commun* 292: 492-497.
3. Kitagawa C, Ando M, Ando Y, Sekido Y, Wakai K, et al. (2005) Genetic polymorphism in the phenobarbital-responsive enhancer module of the UDP-glucuronosyltransferase 1A1 gene and irinotecan toxicity. *Pharmacogenet Genomics* 15: 35-41.
4. Walker (2008) *Pediatric Gastrointestinal Disease*(5)769-771
5. Bancroft JD, Kreamer B, Gourley GR (1998) Gilbert syndrome accelerates development of neonatal jaundice. *J Pediatr*132: 656-660.
6. Matsui K, Maruo Y, Sato H, Takeuchi Y (2010) Combined effect of regulatory polymorphisms on transcription of UGT1A1 as a cause of Gilbert syndrome. *BMC Gastroenterol* 10: 57.
7. Kaplan M, Hammerman C, Maisels MJ (2003) Bilirubin Genetics for the Nongeneticist: Hereditary Defects of Neonatal Bilirubin Conjugation. *Pediatrics* 111: 886-893