

Crigler-Najjar syndrome type 2: Novel UGT1A1 mutation

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Crigler-Najjar syndrome type 2 is a rare cause for persistent unconjugated hyperbilirubinemia, inherited in an autosomal recessive manner. Even though it is compatible with normal life span, in the absence of prompt suspicion and intensive management it can prove fatal not only in the neonatal period but also during adult life. Here, we describe a case with a novel homozygous UGT1A1 p.Pro176Leu mutation.

Key words: Arias syndrome, Crigler-Najjar syndrome type 2, kernicterus, UGT1A1, unconjugated hyperbilirubinemia

Introduction

Crigler-Najjar Syndrome Type 2 is an entity that is very rarely encountered in clinical practice. The condition has to be considered in all cases of severe non-hemolytic unconjugated hyperbilirubinemia in the newborn period. To prevent kernicterus, management should be initiated early with phenobarbitone following the initial control of hyperbilirubinemia with phototherapy or exchange transfusion. Phenobarbitone should be given lifelong, and the patient should avoid drugs that displace bilirubin from albumin. We are presenting a consanguineous family with a 16 year old girl who is being treated with phenobarbitone from birth with partial control of jaundice and a history of early neonatal death of two siblings with jaundice. We have confirmed the diagnosis

by demonstrating a mutation in the UGT1A1 gene (a proline-to-leucine substitution at amino acid position 176 (p.Pro176Leu) encoded by exon 1, for which the patient was homozygous).

Case Report

A 16-year-old girl, who was the fourth child of a third-degree consanguineous couple, was under our follow-up for persistent unconjugated hyperbilirubinemia. She developed neonatal jaundice at 24 h after birth. She has one healthy 24-year-old brother. The second and third siblings also had severe unconjugated hyperbilirubinemia with the onset at 24 hours of life. They, in contrast, developed kernicterus and expired at 10th and 30th neonatal day, respectively. No definitive diagnosis could be made for these children at that point of time.

Our patient was born as full term with a birth weight of 2800 g. There was no blood group incompatibility for the parents. She did not have cephalhematoma or hepatosplenomegaly. She passed pigmented stools and normally colored urine. Her reticulocyte count was only 2%, and the peripheral smear did not show any evidence of hemolysis. Her thyroid function tests were normal. She needed phototherapy from 24 h of life and underwent two exchange transfusions on Days 5 and 20 postnatally. Abdominal ultrasonogram did not reveal any abnormality. Her liver function tests were normal. There was no improvement following cessation of breast feeding for a few days. Serum unconjugated bilirubin fluctuated between 20 and 25 mg% for several days following which it settled to a level of 14 to 18 mg% by the age of 1 month, and the values are remaining in the same range even now. The

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phototherapy could be discontinued by the 30th neonatal day. She received oral phenobarbitone since second neonatal day at a dose of 15 mg/day, and her present dose is 60 mg/day. The serum bilirubin level rose up to 27 mg% during multiple occasions whenever the phenobarbitone treatment was stopped intermittently by the family.

She attained all developmental milestones at an appropriate age. She is not having any neurologic deficit and has normal intelligence. She never required any blood transfusions after the neonatal period.

Based on the disease course and the family history, the provisional diagnosis of Crigler-Najjar syndrome type 2 was entertained. Sequence analysis of all five exons of the *UGT1A1* gene and of the promoter region was performed. This led to the identification of a proline-to-leucine substitution at amino acid position 176 (p.Pro176Leu) encoded by exon 1, for which the patient was homozygous. Parental analysis revealed that her mother was a heterozygous carrier of the P176L exchange and that she also carried a glycine71 → arginine substitution encoded by the other allele, which is the most common mutation resulting in Gilbert's syndrome among Asians.^[1]

Discussion

In 1952, John F. Crigler and Victor A. Najjar described seven patients with congenital familial non-hemolytic jaundice and kernicterus.^[2] Crigler-Najjar syndrome (CNS) is due to the absence (type 1) or deficiency (type 2) of the enzyme UDP-glucuronyltransferase, which is needed for the conversion of bilirubin to water-soluble bilirubin mono- and diglucuronides in hepatocytes, which facilitates its excretion into the bile.^[3,4] In CNS type 1, the affected infant needs daily phototherapy to prevent the development of kernicterus. Phenobarbitone is not beneficial in this condition. Liver transplantation is the only way to cure the disease.^[5] Some studies have shown beneficial effect with orlistat, a drug usually prescribed for weight reduction. This drug when administered orally increases the fecal excretion of unconjugated bilirubin, thereby reducing the enterohepatic circulation.^[6] In CNS type 2 (Arias syndrome), enzyme activity is usually between 10 and 30% of normal, and serum bilirubin ranges between 5 and 25 mg%. Unlike in type 1, there is marked improvement with phenobarbitone. Serum bilirubin can be brought

down to two-thirds of the basal level with this treatment.^[7] Even though the risk is minimal, there are reports of the occurrence of kernicterus, not only in the newborn period but also in adolescents or adults.^[8,9] Continuous use of oral phenobarbitone at a dose of 5 mg/kg/day usually prevents this complication. The risk is higher at times of infection, fasting, dehydration, surgery and trauma or in situations resulting in hypoalbuminemia. Affected patients should also avoid drugs that displace bilirubin from albumin such as penicillines, sulphonamides, salicylates, ceftriaxone and furosemide.

The main differential diagnosis is Gilbert's syndrome, which also is inherited in an autosomal recessive manner. It affects more than 5% of the population. Here, the serum bilirubin will be usually less than 5 mg%. No treatment is needed even though the serum bilirubin level can go beyond this concentration at times of infection and fasting.

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