

Inherited Unconjugated Hyperbilirubinemia: Crigler Najjar Syndrome

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Abstract: CriglerNajjar syndrome is an inherited disorder that manifests as persistent unconjugated hyperbilirubinemia. It occurs due to a defect in bilirubin conjugation due to complete or partial deficiency of uridine 5'-diphosphate glucuronosyltransferase enzyme. It comprises type 1 with complete deficiency and type 2 with partial deficiency of the enzyme. An early diagnosis in CriglerNajjar syndrome type2 enhances life expectancy. We present a 40-day old male child with CriglerNajjar syndrome type 2 with a heterozygous missense mutation in exon 1 of the UGT1A1 gene.

Keywords: CriglerNajjar. Unconjugated hyperbilirubinemia. phenobarbitone

I. Introduction

Crigler Najjar syndrome (CNS) is an autosomal recessive disorder characterised by non-hemolytic unconjugated hyperbilirubinemia^[1]. It has been classified into 2 types based on the degree of unconjugated hyperbilirubinemia and its response to oral phenobarbitone therapy^[2]. CNS type 1 is due to absence and type 2 is due to deficiency of the enzyme UDP-glucuronosyltransferase which facilitates conversion of bilirubin to water soluble bilirubin mono- and diglucuronides in the hepatocytes, thereby promoting its excretion into the bile. We present a para-neonate with prolonged unconjugated hyperbilirubinemia who responded to oral phenobarbitone therapy with a heterozygous missense mutation in exon 1 of the UGT1A1 gene.

II. Case Report

A 40 day old male child born of non-consanguineous marriage, presented to us with yellowish discolouration of eyes and skin since the eighth day of life. He was the only child with an uneventful birth history and was completely immunized for his age. He appeared to be developmentally normal and was exclusively breast fed. On examination, vital parameters were normal and icterus was seen in the upper palpebral conjunctiva, palms and soles. Systemic examination was normal. Laboratory investigations showed total bilirubin-13.6mg/dl, direct bilirubin-0.3mg/dl, indirect bilirubin-13.3 mg/dl. Other investigations including complete hemogram showed haemoglobin-9.2mg/dl, whole blood cell count- $10.3 \times 10^3/\mu\text{L}$ with neutrophils-21.8%, lymphocytes-65.9%, eosinophils-8.4%, red blood cell count- $2.7 \times 10^6/\mu\text{L}$, platelet count- $298 \times 10^3/\mu\text{L}$. The thyroid profile was normal.

Breast milk jaundice was ruled out by stopping breast milk for a period of 7 days with no evidence of decrease in bilirubin levels. Hence, CriglerNajjar workup was performed specially to differentiate the type. A therapeutic trial of phenobarbitone (5mg/kg/day) was administered for 7 days following which a significant decline in the bilirubin levels was recorded, total bilirubin-4.5mg/dl, direct bilirubin-0.6mg/dl, indirect bilirubin-3.9mg/dl, thereby clinching the diagnosis of CriglerNajjar syndrome type II. A mutation analysis of UGT1A1 gene, that expresses bilirubin uridine 5'-diphosphate glucuronyltransferase (UGT) was done to assist the diagnosis, which showed heterozygous missense mutation c.211G>A (p.G71R) in exon 1 which encodes the carboxyl-terminal domain of all UGT isoforms, known polymorphic variant.

III. Discussion

Crigler Najjar syndromes are inborn errors of bilirubin metabolism characterised by unconjugated hyperbilirubinemia due to the defective activity of the hepatic enzyme bilirubin uridine 5'-diphosphate-glucuronyltransferase (B-UGT)^[2]. They are rare group of diseases with an estimated incidence of 1/1,000,000 births^[3]. It was first described by John F. Crigler and Victor A. Najjar in seven patients with congenital familial non-hemolytic jaundice and kernicterus^[4]. CNS type 1 manifests as severe unconjugated hyperbilirubinemia with

high levels of serum bilirubin due to the absence of B-UGT activity, whereas the milder form CNS type 2 is due to decreased B-UGT activity wherein a significant reduction in bilirubin levels is seen in response to oral phenobarbitone therapy^[1].

The enzyme bilirubin uridine diphosphate-glucuronosyltransferase (*ugt1a1*) mediates bilirubin glucuronidation, thereby promoting efficient biliary excretion of bilirubin^[5]. *ugt1a1* is encoded by five exons of the UGT1A1 gene. Defects in *ugt1a1* gene result in non-hemolytic unconjugated hyperbilirubinemia including CriglerNajjar syndrome and Gilbert syndrome. Literature review shows that exons 1 and 5 are the hotspot regions of the UGT1A1 gene in Asian populations and that p.G71R and p.Y486D are the two most common variants leading to *ugt1a1* genetically-associated unconjugated hyperbilirubinemia^[6]. Mutation analysis in our case also showed a heterozygous missense mutation p.G71R in exon 1 of the *ugt1a1* gene.

In CNS type 2 also known as Arias syndrome, the enzyme activity ranges between 10 to 30% of normal and serum bilirubin ranges between 5 and 25 mg%^[4]. The continuous use of oral phenobarbitone (5mg/kg/day) not only reduces the bilirubin levels to two-thirds of the normal but also prevents grave morbidities like kernicterus. A cost-effective approach would be a therapeutic trial of phenobarbitone and repeating the investigations. However, to have a robust scientific study, it would be pertinent to do an exon analysis and to learn about a new mutation.

IV. Conclusion

To conclude, unconjugated hyperbilirubinemia in a paraneonate besides breast milk jaundice, CriglerNajjar syndrome is a strong possibility with the simple method of a therapeutic trial of oral phenobarbitone to differentiate between the 2 types.

References

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