CASE REPORT

CRIGLER NAJJAR SYNDROME TYPE I, A RARE BUT SEVERE CAUSE OF UNCONJUGATED HYPERBILIRUBINEMIA IN CHILDREN

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ABSTRACT

Crigler Najjar Syndrome Type I is a rare and severe autosomal recessive disorder of bilirubin metabolism. It has been associated with consanguinity in some patients. Infants without any evidence of hemolysis, develop severe, permanent, unconjugated hyperbilirubinemia within the first few days of life resulting in chronic kernicterus.

INTRODUCTION

This rare and severe autosomal recessive disorder of bilirubin metabolism occurs with an incidence of 0.6–1.0 per million live births. Occurs in all races and has been associated with consanguinity in some patients (1).It is characterized by non-hemolytic unconjugated hyperbilirubinemia. According to serum total bilirubin concentration (STBC), Crigler Najjar Syndromes (CNS) is classified into two types: type I (CNS-I), in which the STBC is more than 25 times that of the normal level ranging from 342 to 684 μmol/L, and type II (CNS-II), in which it is 6-25 times with a range of STBC within 103-342 μmol/L [2,3].

In 2002, Al Shurafa et al. analyzed the outcome of six children with Crigler-Najjar Syndrome type I & reported. The first three had living-related liver transplants in Saudi Arabia and the Middle East. Two developed acute hepatocellular rejection, (treated with methylprednisolone pulse therapy) & one had a biliary leak (surgically repaired). Post-op bilirubin levels returned to normal in all three and no further phototherapy was required (4).

Few hundred cases reported since the first report in 1952 by Crigler and Najjar in six infants in three families. All six infants developed severe, permanent, unconjugated hyperbilirubinemia within the first few days of life, without any evidence of hemolysis. Five of the six infants died of kernicterus by the age of 15 months (1).

The sixth infant was free of neurologic disease until 15 years of age, when kernicterus suddenly developed in adolescent and died six months later (1).

CASE REPORT

A 2-year and 4 months old female presented with jaundice noticed since 10th day of life and presented to Tikur Anbessa Specialized Teaching Hospital. Pregnancy and delivery history was unremarkable. Physical examination showed no dysmorphic features, stable

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vital signs, and anthropometric measurements were normal for her age, had deep icteric sclera and skin, no pallor had hepatomegally of 4cms below the right costal margin with total liver span of 10cms but no splenomegally. She was assessed with a modified Glasgow Coma Scale and it was 3/5, muscle tone was normal.

INVESTIGATIONS

Total serum Bilirubin 34, direct 22 (almost all the time) T3, T4, TSH- Normal, VDRL, Nonreactive, DNA PCR negative, CMV, toxoplasmosis all were non revealing, liver enzymes and liver function tests were normal, hepatitis viral markers (HBSAg, anti HCV antibody and HAV antibody) were negative. U/S- Normal, no evidences of biliary atresia, and choledochal cyst.

She was on follow up at the pediatrics gastroenterology/ hepatology clinic and periodic phototherapy was given. While on follow-up, she developed altered mentation and abnormal body movement since 1 yr and 8 months of age. At which time patient was referred and went to America for genetic analysis.

Genetic analysis showed UGT1A1 mutations deserted in association with CN I have included nonsense, frame shift and missence mutations which is indicator of homozyosity. Crigler Najjar Type II patients typically have 2 missence mutations, but may also be compound heterozygous for one missence and one nonsense frame shift mutation. The finding fits best for CN(Crigler Najjar type I)

DICUSSION

CNS I should always be suspected in infants who developed persistent jaundice due to unconjugated bilirubin within the first few days after birth. These children have normal liver function test, may have neurologic symptoms due to kernicterus. Occasionally, late onset kernicterus in adolescence may be possible.

The hallmark of CNS I is pure unconjugated hyperbilirubinemia, ≈ 20 to 25 mg/dl but can be as high as 50 mg/dL. Stool color is normal, but fecal urobilinogen excretion is diminished due to the marked reduction in the conjugation of bilirubin and rate of bilirubin production, bone marrow morphology, and RBC morphology and survival are normal.

Prenatal diagnosis and genetic counseling are recommended because of the high frequency of consanguinity. Inhibitors of heme-oxygenase, such as tin-protoporphyrin or tin-mesoporphyrin, results in marked inhibition of the enzyme activity in various organs. A single dose of tin-mesoporphyrin administered in neonates, shortly after birth, resulted in an average of 76% reduction of bilirubin and abolished need for phototherapy (5).

Histopathology findings are nonspecific on light and electron microscopy. Exclusion of other persistent unconjugated hyperbilirubinemia conditions in infancy is necessary. In our case, 2 years and 4 months old female child who had no response for phototherapy and early phenobarbitone, genetic analysis revealed Crigler Najjar syndrome type I.

A liver transplant is the only definitive treatment for Crigler-Najjar syndrome type I. It rapidly normalizes bilirubin levels. Despite its risks, some advocate prophylactic liver transplantation to avoid the risk of kernicterus which may not be fully reversible once it is established. Hepatocyte transplantation is a promising alternative (6)

CONCLUSION

Definitive diagnosis can be made by in vitro expression of mutant DNA from patients but this method is too elaborative and expensive for routine use. UGT1A1 mutations deserted in association with CNS I has included nonsense, frame shift and missence mutations. Patients with type II CN, typically have 2 missence mutations, but may also be compound heterozygous for one missence and one nonsense frame shift mutation.

Taking the poor response for medical treatment (medical history) and genetic analysis, this patient is a real case of Crigler Najjar syndrome type I.

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