

Case Report

A case of jaundice associated with hypertrophic pyloric stenosis carrying UGT1A1 polymorphism

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This work was conducted at Ege University Hospital School of Medicine.

Accepted 26 April, 2010

To demonstrate the UGT1A1 (TA)₇ TAA polymorphism in a 45 day old boy with jaundice and recurrent vomiting caused by hypertrophic pyloric stenosis. A 45-day-old boy was brought to the emergency department with vomiting and jaundice. On admission, the baby was icteric and had weight lost. No evidence of infection and hemolysis. His thyroid function tests and all other biochemical tests were normal except for serum total bilirubin level which was measured as 9.82 mg/dl, with an unconjugated fraction as 9.05 mg/dl. DNA analysis was performed and the heterozygous (TA)₇TAA polymorphism was revealed in the bilirubin uridine diphosphate glucuronosyl transferase gene (UGT1A1) of the patient. Sonographic image revealed that hypertrophic pyloric stenosis. Ramsted pyloromyotomy was performed by pediatric surgery department. The jaundice disappeared within two days and the infant was discharged. We recommend that it is crucial step to care in a neonate with jaundice, recurrent vomiting and especially weight loss. Although hypertrophic pyloric stenosis and Gilbert Syndrome seem two different conditions, in selected patients more laboratory test should be obtained for differential diagnosis.

Keywords: Hypertrophic pyloric stenosis (HPS), Gilbert, jaundice, infants

INTRODUCTION

Neonatal jaundice is a condition which is sometimes observed in infants with hypertrophic pyloric stenosis (HPS). Previous reports favored the hypothesis that such cases could represent as early manifestation of Gilbert's syndrome (GS) (Alagille and Odièvre, 1979; Bosma et al., 1995; Trioche et al., 1999). This benign condition has shown to be due to a polymorphism in a promoter of the bilirubin UDPglucuronosyltransferase (UDP-GT) gene (UGT1A1), with seven instead of six TA repeats in this region (6,9). It is important to pay attention in a newborn with jaundice, recurrent vomiting and especially weight loss to think and to investigate clinical and laboratory findings of HPS and possibility of GS and relationship between those two different conditions. We report here a case of jaundice associated with hypertrophic pyloric

stenosis carrying UGT1A1 polymorphism.

CLINICAL PRESENTATION AND INTERVENTION

A 45-day-old boy was admitted to the emergency department because of recurrent vomiting after feeding and weight loss. He was born after an uneventful pregnancy at term. Birth weight was 3700 g; he had no history of jaundice during neonatal period. His parents were healthy and unrelated, mother's age was 32 and their previous child had been diagnosed to have Down syndrome. Additionally he had had endocardial cushion defect, tetralogy of Fallot, pulmonary stenosis and hypothyroidism. This child had died because of surgical complications after cardiac surgery at the age of 6 months.

On admission, the physical examination of the baby revealed that his weight was 4000 g (50th centile), length 54 cm (50th centile), and he was icteric. He had projectile vomiting especially in a short period after feeding.

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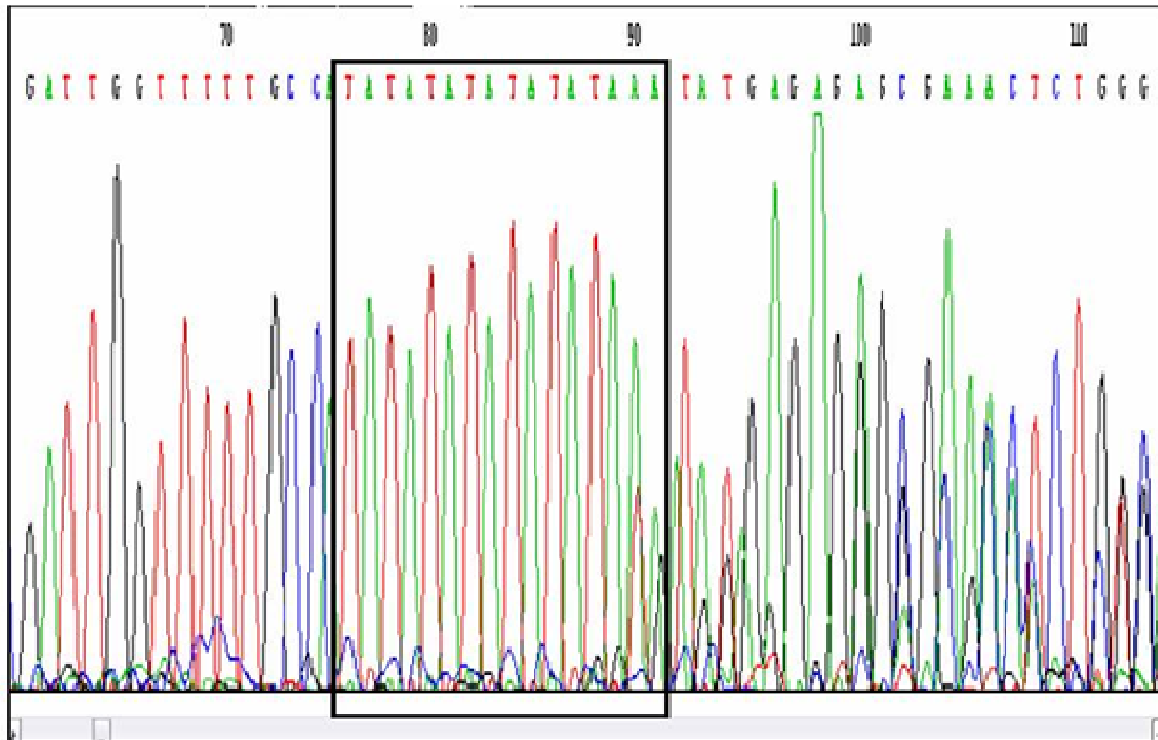


Figure 1. Sequencing of the UGT1A1 promoter region

Otherwise, he was normal. There was no evidence of infection and hemolysis. His thyroid function tests and all other biochemical tests were normal except for serum total bilirubin level which was measured as 9.82 mg/dl, with an unconjugated fraction as 9.05 mg/dl. Within the first 15 days of hospitalization period projectile vomitings continued and he lost 900 g, became dehydrated and his icterus increased.

On inverted sonographic image of the patient; long axis of pylor was measured 5 mm along 21 mm length and was diagnosed as hypertrophic pyloric stenosis. He was consulted by department of pediatric surgery and Ramsted pyloromyotomy was performed. The jaundice disappeared within two days and the infant was discharged.

Since there have been a number of studies reporting the relationship between jaundice observed in babies with pylor stenosis and (TA)7TAA polymorphism in the bilirubin uridine diphosphate glucuronosyl transferase gene (UGT1A1), DNA analysis was performed and the heterozygous (TA)7TAA polymorphism was revealed in the bilirubin uridine diphosphate glucuronosyl transferase gene (UGT1A1) of the patient.

DISCUSSION

Neonatal jaundice is sometimes seen in infants with hypertrophic pyloric stenosis. Previous reports have

determined that such cases hyperbilirubinemia could represent as early manifestation of Gilbert syndrome (GS) (Alagille and Odièvre, 1979). Clinical features common to both GS and ictero-pyloric syndrome (IPS) include jaundice provoked by fasting and improved with feeding. In 1995, a genetic mutation with seven instead of six TA repeats in the pro-moter region of the UGT1A1 gene (Bosma et al., 1995; Monaghan et al., 1996) was found to be associated with GS.

Trioche et al (1999) reported a case series in three infants; two were homozygous for a (TA) 7TAA polymorphism, one patient was heterozygous for the same polymorphism (Trioche et al., 1999). Their control patients had hypertrophic pyloric stenosis without jaundice. They found as homozygous for the (TA) 6TAA sequence and judged normal. Some data demonstrate that increase of the promotor TATA box binding site causes decreasing of the enzyme activation as well as bilirubin conjugation (Bosma et al., 1995). These findings recommend that there is an association between the promoter polymorphism of the UGT1A1 gene and jaundice associated with hypertrophic pyloric stenosis. This condition can be explained by either homozygous or heterozygous (TA) 7TAA polymorphism.

In the present case direct sequencing analysis of the promoter region of UGT1A1 gene revealed a genotype of (TA) 6/7TAA in the patient (Figure 1). The parents were also sequenced for the same region and the mother was found to be heterozygous for the same polymorphism

((TA) 6/7TAA) whereas the father was (TA) 6/6TAA. She had no history of icteric episodes. However, in her medical history she had a complaint of paleness and minimal icteric appearance after hard working. On the other side she was HBV carrier and we examined her serological and biochemical analysis as normal.

In a retrospective study, Liu Hua and co-workers (Hua et al., 1966) reported that the prevalence of IPS in infants with HPS. The role of illness severity in the etiology of IPS, and the role of the common genetic mutation for GS (UGT1A1*28) in the etiology of IPS were also sought. They identified that the risk of having a GS genotype was 4.1-fold higher in IPS than HPS. The exact pathogenesis is unknown. However, jaundice in HPS may be explained by having dehydration, mechanical obstruction, decreased carbohydrate and hepatic perfusion, or a combination of the above mechanisms (Garrow and Hertzler, 1966)

The prevalence for genetic mutation of GS is previously reported to be 10-19%. The physical examination of GS is usually unrevealing except for icterus. GS with icterus ranges between 3-10%. Several factors such as increasing bilirubin load, impaired hepatic uptake of bilirubin, impaired efficiency of glucuronidation required to make clinically apparent GS. It is rarely diagnosed prior to puberty when alterations in sex steroid concentrations affect bilirubin metabolism, leading to increased plasma bilirubin concentrations however, more recent data suggest manifestation in the neonatal period (Aono et al., 1995; Chowdhury, 1994; Garrow and Hertzler, 1996; Owens and Evans, 1975). Despite the more rapid rise in neonatal period of our case, his mother's condition appears to be a typical clinical manifestation of GS, which is seen in late decades.

Conclusion

It is important to care in a newborn with jaundice, recurrent vomiting and especially weight loss. Although HPS and GS seem two different conditions, in selected

patients more laboratory test should be obtained for differential diagnosis.

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