A Case of Gilbert’s Syndrome with Severe Neonatal Hyperbilirubinemia

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Gilbert’s syndrome is caused by a reduction in the activity of uridine diphosphate glucuronosyltransferase (UGT) and induces chronic, non-hemolytic unconjugated hyperbilirubinemia. It has been suggested that 3-10% of the population has Gilbert’s syndrome. Commonly, Gilbert’s syndrome causes mild symptoms. However, a case of Gilbert’s syndrome with severe neonatal hyperbilirubinemia is presented here. The patient developed jaundice three days after birth. Five days after birth, the patient’s total serum bilirubin level was 34 mg/dL. The patient received intensive phototherapy and was given oral phenobarbital. Hemolytic hyperbilirubinemia was excluded on the basis of laboratory tests. Heterozygote polymorphisms of the promoter region (-3279T>G) and exon 1 (211G>A) were found in UGT1A1 gene. After discharge, the patient did not require any further treatment. This is the first case of proven Gilbert’s syndrome with severe neonatal hyperbilirubinemia in Korea.

Key Words: Gilbert disease, Gilbert’s syndrome, Newborn, Hyperbilirubinemia

Introduction

Gilbert’s syndrome is a chronic, non-hemolytic unconjugated hyperbilirubinemia caused by a reduction in the activity of uridine diphosphate glucuronosyltransferase (UGT). UGT plays a critical role in the detoxification of bilirubin by conjugating it with glucuronic acid1-3. Three grades of UGT1A1 deficiency occur in humans: Crigler-Najjar syndrome type 1, 2, and Gilbert’s syndrome. Among these, Gilbert’s syndrome is the mildest form. In patients with Gilbert’s syndrome the serum bilirubin levels fluctuate from normal to 5 mg/dL. The levels may be higher in the presence of hemolysis and increase with fasting, stress or infection4). In most cases of Gilbert’s syndrome the symptoms are mild, but it may be associated with exaggerated neonatal jaundice5). Here, a case of Gilbert’s syndrome in a neonate with severe hyperbilirubinemia is reported.

Case report

A 5-day-old girl was admitted via the outpatient department with a yellowish change of skin color two days prior to admission. Her activity and crying were not decreased. On the physical examination, the weight was 3,430 g and the height 51 cm. The pulse rate was 145/min, the respiratory rate was 45/min, and the body temperature was 36.8℃. The patient had icteric sclera and face, abdomen and feet. Laboratory studies revealed a hemoglobin level of 15.9 g/dL, a white blood cell count of 12,200/mm³, and a
platelet count of 381,000/mm³. The reticulocyte count was 3.3% and the corrected reticulocyte count was 3.4%. The total serum bilirubin level was 34 mg/dL, direct bilirubin was 1.4 mg/dL, aspartate aminotransferase was 30 U/L, alanine aminotransferase was 11 U/L and gamma-glutamyltransferase was 43 U/L. The electrolyte levels were within normal ranges. Viral serology (toxoplasma, rubella, cytomegalovirus, herpes simplex and syphilis) was not performed, but blood and urine cultures were normal. Abdomen and brain ultrasonography were performed, and the results were normal. The blood type was B Rh positive and her mother’s blood type was O Rh positive. The peripheral blood smear findings showed no evidence of hemolytic anemia. The result of Coombs’ test was negative. Overt hemolysis was excluded on the basis of normal hemoglobin values, reticulocyte counts, and the results of peripheral blood smear and direct Coombs’ test.

An intensive phototherapy was started, and the total serum bilirubin level was assessed every three to four hours on the first hospital day. The total serum bilirubin level fell to 29.7 mg/dL after three hours of treatment and to 28.4 mg/dL after four hours of further treatment. On the second hospital day, the total serum bilirubin level was 24.6 mg/dL. The patient was also treated with oral phenobarbital in addition to the intensive phototherapy. The total serum bilirubin level decreased gradually afterward. The level was 10.2 mg/dL on the seventh hospital day, finally falling to tolerable levels. The patient was discharged without medication after stabilization of the total serum bilirubin level. The total serum bilirubin level has remained below 1 mg/dL, despite infection such as acute bronchiolitis and a urinary tract infection.

Genetic studies were performed for the evaluation of the cause of the severe hyperbilirubinemia. Genomic DNA was isolated from lymphocytes, and the exons and the promoter regions of the UGT1A1 gene were amplified using polymerase chain reaction. Mutation analysis of the UGT1A1 gene revealed that the patient had compound heterozygosity for two different polymorphisms in the promoter region (-3279T>G) and in exon 1 (211G>A) (Fig. 1).

**Discussion**

The reduction of UGT1A1 activity causes unconjugated hyperbilirubinemia as observed in the Crigler–Najjar syndrome and Gilbert’s syndrome. The mutations of the UGT1A1 gene are associated with clinical hyperbilirubinemia. Genetic abnormalities causing an absence of UGT1A1 activity result in Crigler–Najjar syndrome type 1, which is characterized by potentially lethal hyperbilirubinemia. In addition, mutations causing a severe but incomplete reduction of UGT1A1 activity result in Crigler–Najjar syndrome type 2, which is characterized by intermediate levels of hyperbilirubinemia. In Gilbert’s syndrome, UGT1A1 activity is reduced to approximately 30% of the normal levels. Gilbert’s syndrome is characterized by a mild and chronic unconjugated hyperbilirubinemia2, 6, 7). However, it may be associated with exaggerated neonatal hyperbilirubinemia if other risk factors such as prolonged fasting, surgery, and infection are present. The UGT1A1 gene consists of a promoter region and exon region. A mutation of the promoter region is principally known to be associated with Gilbert’s syndrome, and a mutation of the exon region is known to be associated with Crigler–Najjar syndrome. However, UGT1A1 mutations are appeared to be variable among different ethnic groups6, 8). A part of exon 1 containing the 211G>A (G71R) has been reported to be
associated with Gilbert’s syndrome in the Asian population, while Gilbert’s syndrome in Caucasians is more commonly associated with the TA7 mutation. In this case, heterozygous polymorphisms were identified in the UGT1A1 gene promoter (-3279T>G) region and exon 1 (211G>A) region, which has previously been reported to be associated with Gilbert’s syndrome in the Asian population. Gilbert’s syndrome is commonly associated with mild symptoms. However, in this case, severe neonatal jaundice developed. Hemolysis and inflammation were excluded. Liver enzyme was normal. But less frequent causes of unconjugated hyperbilirubinemia, such as ineffective erythropoiesis, cardiac disease, rhabdomyolysis and drugs were not evaluated. In Crigler-Najjar syndrome type 1, treatment with exchange transfusions is effective and liver transplantation is the only definitive therapy. In Crigler-Najjar syndrome type 2, continuous treatment with phenobarbital is usually needed. The -3279T>G mutation of UGT1A1 reduces transferase activity to 40% of the normal level. This mutation in Crigler-Najjar syndrome type 2 has been previously reported. The hyperbilirubinemia associated with the -3279T>G mutation responds well to phenobarbital treatment. This patient was treated with short-term intensive phototherapy and phenobarbital. The severe jaundice shown in this patient had features similar to Crigler-Najjar syndrome which was initially suspected. However, the benign course was similar to Gilbert’s syndrome, which was the final diagnosis.

The heterozygous mutations of -3279T>G and 211G>A may cause severe neonatal jaundice as observed in this case. Because the -3279T>G mutation responds well to phenobarbital treatment, it is reasonable to start phenobarbital during the early course of treatment with intensive phototherapy for neonatal jaundice of unknown etiology in the Asian population.

한글요약
Gilbert 증후군(Gilbert’s syndrome)은 빌리루빈이 체외배설을 위해 포함시키는 기능을 가진 효소인 uridine diphosphate glucuronosyltransferase (UGT)의 활성을 감소에 의해 야기되며 만성, 비용혈성, 비포합 고빌리루빈혈증을 유발한다. 대부분 경증의 증상을 보이며 인구의 3-10%에서 나타나는 것으로 알려져 있다. 치료로 페노바비탈(phenobarbital)을 투여할 수 있으며 이 페노바비탈은 UGT 효소활성도를 증가시키며 혈중 빌리루빈 농도를 떨어뜨린다. 본 증례에서는 일반적인 경우와 달리 심한 신생아 황달이 동반된 Gilbert 증후군을 기술하였다. 환아는 생후 2-3일경부터 황달 소견을 보였으며 생후 5일경 혈중 총 빌리루빈 수치가 34 mg/dL로 높게 상승되어 있어 집중적인 광선치료의 시행과 함께 정구 페노바비탈을 투여 받았다. 감사실 소견에서 정상 혈색소, 망상적혈구 수치 보였으며 direct Coombs’ test에서도 정상 소견 보여 용혈성 고밀리루빈혈증은 제외하였으며 이후 시행한 유전자 검사에서 UGT1A1 유전자의 -3279T>G, 211G>A 변이가 발견되어 Gilbert 증후군으로 진단되었다. 광선치료와 정구 페노바비탈 투여로 혈중 총 빌리루빈 농도의 지속적 감소를 보여 퇴원하였으며 이후 외래검사상 총 빌리루빈 수치는 안정적이었다. 저자들은 심한 신생아 황달을 보인 Gilbert 증후군의 예를 보고하는 바이다.

References

