To the Editor:

Hereditary spherocytosis (HS) is a common inherited hemolytic anemia with a prevalence of at least 1 in 5,000 people. The clinical features of HS are anemia, jaundice, and splenomegaly. The clinical forms in adulthood are mild, typical, and severe. However, HS is commonly symptomatic in the neonatal period (65% of cases). Jaundice is the first and more frequent symptom, often requiring phototherapy and sometimes exchange-transfusion.

The presence of neonatal symptoms is not strictly predictive of the adult form, nor is it associated within specific erythrocyte membrane alteration. Hemolysis in the neonatal period has been partially attributed to the presence of free 2,3-diphosphoglycerate (2,3-DPG) which further destabilizes the membrane skeleton. The worsening of the jaundice is also due to the interaction between hemolysis of spherocytes and the reduced capacity of the neonatal liver to conjugate bilirubin.

Gilbert’s syndrome is a benign unconjugated hyperbilirubinemia characterized by episodes of mild intermittent jaundice. It is the most common inherited disorder of hepatic bilirubin metabolism, occurring in 2% to 13% of the population. Recently a correlation between homozygosity for a 2-bp insertion in the promoter of the UDP-glucuronosyltransferase 1 (UGT1) exon 1 and Gilbert’s syndrome was demonstrated. This insertion lies within the TATA box sequence and causes a less efficient binding of transcription regulatory proteins. Hepatic glucuronidating activity is reduced to about 30% of normal.

We examined retrospectively 178 newborns affected with HS (98 males and 80 females); all were at term and their weight ranged between 3,000 and 3,500 g. 160 of 178 newborns were breast fed. Diagnosis of HS was performed by means of osmotic fragility test and red blood cell protein assay. Analysis of the presence of two (TA) extranucleotide elements in the promoter of UDP1 gene was performed by means of polymerase chain reaction and analysis of the amplified DNA fragments in a 6% polyacrylamide gel. Analysis of bilirubin level was performed daily during the first week of life. Hyperbilirubinemia was classified as a total bilirubin level higher than 2 SD of normal value and these levels were required phototherapy. We excluded all the newborns affected by infections or presenting any illness associated with increased bilirubin levels.

According to the UDP1 genotype, two groups of subjects were identified: the first was composed of 148 6/6 [homozygotes for the common allele] bearing the sequence (TA)6[TAA] or 6/7 genotype; whereas the second group was composed by 30 individuals homozygous for the sequence (TA)7[TAA].

The frequency of 7/7 genotype in the Italian population was 16.9%, higher than that observed in Northern European population. In the examined HS population 112 (63%) patients added phototherapy during the first days of life. Jaundice requiring phototherapy was present in 97% of HS patients homozygous for Gilbert’s gene, whereas about one half on the patients with at least one UDP1 normal gene had total bilirubin levels not higher than 2 SD of normal value (Table 1).

Certainly the increased clinical manifestation of HS in neonatal period is a very complex process in part due to the intracellular metabolic causes; however, our results suggest that the genetic variation in bilirubin UDP1 gene promoter plays a role in the enhanced clinical manifestation (jaundice) of HS newborns.

A. Iolascon
M.F. Faienza
A. Moretti
Dipartimento di Biomedicina dell’Età Evolutiva
Università di Bari
Bari, Italy

S. Perrotta
E. Miraglia del Giudice
Dipartimento di Pediatria
II Università di Napoli
Napoli, Italy

REFERENCES


UGT1 Promoter Polymorphism Accounts for Increased Neonatal Appearance of Hereditary Spherocytosis

A. Iolascon, M.F. Faienza, A. Moretti, S. Perrotta and E. Miraglia del Giudice