Research Letters

Polymorphic Variants of UGT1A1 in Neonatal Jaundice in Southern Brazil

Summary

Alterations in the hepatic conjugation of bilirubin due to uridyly-diphosphate-glucuronosyltransferase 1A1 (UGT1A1) polymorphisms have been proposed as risk factors to neonatal jaundice. Herein, we estimated the frequency of genotypes of the promoter region of UGT1A1 gene in newborns and evaluated its association with severe hyperbilirubinemia. Prospective study of cases and controls including all newborns admitted for phototherapy at HCPA, Brazil, during 9 months; 490 babies were enrolled and PCR was performed. Polymorphic genotypes were detected in 16% of the patients and 7 of the 10 possible genotypes were identified with higher prevalence of polymorphisms in Afro-descendants. In this sample, the variants of UGT1A1 were not associated to severe hyperbilirubinemia; other genic factors should be sought in this high miscegenation area of Brazil.

Key words: UGT1A1, neonatal jaundice, hyperbilirubinemia, glucuronyl transferase, genetic variations.

Neonatal jaundice must be monitored to identify babies at higher risk of encephalopathy. The association of known factors with abnormalities in hepatic conjugation of bilirubin as in Gilbert’s syndrome (GS) was proposed in those cases [1–3]. Polymorphic genotypes of uridyly-diphosphate-glucuronosyltransferase 1A1 (UGT1A1) enzyme are characterized by variations in the promoter region sequence of the gene. In GS, there is an extra pair of TA bases in element TATAA of the gene promoter, originating genotype (TA)7/(TA)7 instead of wild (TA)6/(TA)6 [4]. Alleles (TA)5 and (TA)8 were also associated with hyperbilirubinemia [5].

This study determined the frequency of alleles and genotypes of the promoter region of the UGT1A1 enzyme gene in newborns and estimated their association with severe hyperbilirubinemia.

Methods

A study of cases and controls including all newborns admitted between March and December 2007 for phototherapy at the Neonatology Service of Hospital de Clínicas de Porto Alegre, Brazil, over 35 weeks of gestational age and weight >2000g. DNA was extracted and polymerase chain reaction (PCR) [6] with primers 5’-GTCACGTGACACAGTCAACAC-3’ and 5’-TTTGCTCTCTGCAGAGGT-3’ marked with fluorescein amidite (FAM) was performed and analyzed by capillary electrophoresis; sizes of amplified sequences were calculated through GeneMapper® program (Applied Biosystems Inc. – Foster City, California, United States). Data were tested by chi-square, Student’s t-test, analysis of variance (ANOVA) and Mann–Whitney U-test (α = 0.05, power = 80%).

Results

A total of 490 neonates were included and the four alleles previously described were identified, frequency of 1.6% for (TA)5, 34% for (TA)7 and 1% for (TA)8. There were 7 of the 10 possible UGT1A1 genotypes identified; those related to GS were present in 15.8% subjects – 11.6% homozygote (TA)7, 1% (TA)7/(TA)8, 1.9% (TA)5/(TA)6 and 1.3% (TA)5/(TA)7.

Prevalence of GS genotypes was 13.5% in icteric and 18.2% in normal patients, p = 0.08. As to ethnic groups, 86.6% of Caucasians showed ‘low risk’ genotypes, and 13.4% GS genotypes, while among blacks, 34% showed GS genotypes and 76%, ‘low risk’ (p = 0.001). Grouping blacks and mulattos in a single category, those GS genotypes were present in 24.5% (p = 0.014). Allelic frequency according to ethnic groups is seen in Table 1.

Discussion

TABLE 1

<table>
<thead>
<tr>
<th>Allele</th>
<th>Whites n (%)</th>
<th>Afro-descendants n (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>(TA)5</td>
<td>10 (1.4)</td>
<td>5 (2.3)</td>
<td>NS</td>
</tr>
<tr>
<td>(TA)6</td>
<td>477 (66.6)</td>
<td>111 (52.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>(TA)7</td>
<td>225 (31.4)</td>
<td>91 (43)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>(TA)8</td>
<td>4 (0.6)</td>
<td>5 (2.4)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Number in between parentheses = number of alleles.

*Total number of alleles 716/total number of alleles 212.

NS, not significant.
Frequency of genotype (TA)7/(TA)7 was 11.6%; in Spain and Portugal it was 10% [7, 8], but in Italy it was 15% [9]. Another Brazilian study indicated 12.5% [10].

Alleles (TA)5 and (TA)8 were described as rare in Caucasian individuals [8, 11] but were found in both populations in Brazil [10]. In Nigerian neonates [12], the frequency of (TA)7 was similar to our black and mulatto babies, but the remaining alleles were different, probably due to the methodologies employed and also the miscegenation in South of Brazil–African, Portuguese, Spanish, German and Italian, followed by Polish, Jewish, Syrian, Lebanese and Japanese [13].

In these icteric patients, prevalence of GS genotypes was lower than in controls as occurred in Italy, Spain and Turkey [14–16]. It was showed [2] that neither GS variants nor glucose-6-phosphate-dehydrogenase deficiency would develop jaundice alone. This was more likely to occur in combination; one study [17] showed the co-expression of UGT1A1 variants with carrier enzyme polymorphisms.

In this sample, the presence of polymorphic variants of UGT1A1 could not be associated with severe hyperbilirubinemia possibly due to the high miscegenation found in Brazil thus other genetic interactions should be studied.

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