IJN
Iranian Journal of Neonatology
http://ijn.mums.ac.ir

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Original Article

Clinical Significance of OATP2 Gene Variants in Iranian Neonates with Hyperbilirubinemia

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ABSTRACT

Background: Neonatal hyperbilirubinemia is a life-threatening and multifactorial disorder affecting about 60%-80% of newborns during their first week of life. Various environmental and genetic factors can contribute to the occurrence of this problem. The present study aimed to investigate the relationship between the two organic anion transporter 2 (OATP2) gene polymorphisms (388A>G and 521T>C) and the risk of neonatal hyperbilirubinemia.

Methods: A total of 200 neonates, including 100 infants with pathological icterus without a specific cause as the case group and 100 healthy neonates as the control group, were included in this cross-sectional study. Using fresh blood DNA, allelic frequency and genotypic distribution of each variant were determined by polymerase chain reaction-restriction fragment length polymorphism method. The biochemical measurements were also performed for both groups.

Results: The two groups were similar in terms of gender, birth weight, gestational age, diet, and type of feeding. Allelic frequency and genotype distribution of the 388A>G and 521T>C polymorphisms did not show any significant association with hyperbilirubinemia both in crude and modified conditions (P>0.05). Moreover, no significant difference was observed between cases and controls in diplotypes and haplotypes analysis (P>0.05).

Conclusion: As evidenced by the obtained results, the neonates with hyperbilirubinemia were not different from healthy newborns in allelic frequency and genotypic distribution of the two variants of the OATP2 gene. It seems that these two polymorphisms are not correlated with the risk of hyperbilirubinemia in an Iranian neonatal population. Further studies with larger sample sizes are needed to confirm the results of this study.

Keywords: Neonatal hyperbilirubinemia, OATP2 gene, Polymorphism, 388A>G, 521T>C

Introduction

Neonatal hyperbilirubinemia (NHB) is one of the most commonly observed disorders in newborns. Total serum bilirubin levels above 5 mg/dl on the first day after birth, 10 mg/dl on the second day, and 12-13 mg/dl on the other day cause NHB (1, 2). Nearly 28% of term neonates (≥37 weeks gestational age) develop NHB, while this percentage increases in preterm neonates (3, 4). The NHB is associated with an increased risk of neurodevelopmental disorders, abnormalities, and infant hospitalization during the first year after birth (3, 5). The NHB can be managed by various treatments, such as phototherapy and exchange transfusion (1, 5-11).

The previously conducted studies have demonstrated that the elevation of unconjugated bilirubin can be affected by various factors, including breastfeeding, premature birth, infection, blood group and Rh incompatibility, glucose-6-phosphate dehydrogenase deficiency (G6PDD), as well as some genetic factors, such as UDP-glucuronosyltransferase 1A1 and organic

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Please cite this paper as:
Boskabadi A, Mamouri G, Boskabadi H, PourAlizadeh N, Moradi A, Mehrad-Majd H. Clinical Significance of OATP2 Gene Variants in Iranian Neonates with Hyperbilirubinemia. Iranian Journal of Neonatology. 2022 Jan: 13(1). DOI: 10.22038/IJN.2021.57052.2074

anion transporter 2 (OATP2) gene (7, 12-14). It has been established that OATP2 is responsible for transporting organic anions to liver cells. Some studies have suggested that OATP2 plays a role in the transmission of both conjugated and unconjugated bilirubin (2, 13). Nonetheless, some reports have proposed that it is not sufficient for bilirubin transportation (15). Although the OATP2 gene has different variations at nucleotides 388, 463, 521, 571, 597, and 1463, some studies have revealed that 388A>G and 521T>C were most effective in different populations with NHB (8, 13, 16-18). Variant 388A>G may reduce the unconjugated bilirubin destruction mechanism by converting aspartic acid to asparagine. It can cause severe hyperbilirubinemia in neonates who are breastfed (13). Mutations at nucleotides 521 also cause NHB by limiting the bilirubin absorption by the liver (19).

The reason for NHB has not been determined in the majority of reported cases. It is still unclear whether there is a relationship between NHB and variants of the OATP2 gene (6, 20). There is a paucity of studies assessing the effect of OATP2 variants on NHB; moreover, reports from different neonatal populations yielded inconsistent results regarding the association between 388A>G and 521T>C variants of the OATP2 gene and risk of NHB (13, 16, 19). In addition, no similar study has been performed on the relationship between this gene and NHB in the Iranian population. In light of the aforementioned issues, the present study aimed to investigate the relationship of NHB with 388A>G and 521T>C variants of the OATP2 gene in an Iranian neonatal population.

Methods

According to the estimated sample size based on the allelic frequencies in a previous similar study (17), a total of 200 term neonates born or hospitalized in Ghaem and Imam Reza Hospitals, Mashhad, Iran, were enrolled in this cross-sectional study from December 2016 to February 2018. The neonates were assigned to two groups based on their serum bilirubin level: neonates with pathological icterus without a specific cause (n=100) as the case group and healthy controls (n=100). Neonatal hyperbilirubinemia was defined based on American Academy of Pediatrics (AAP) guidelines and hour-specific total serum bilirubin (TSB) risk nomogram (21). The control group consisted of neonates with serum TB levels below the 40th percentile according to the Bhutani nomogram (22). Serum TB levels and G6PD enzyme activity were measured by the spectrophotometric method as described earlier (23). The inclusion criteria were: gestational age≥38 weeks, neonate age≤30 days, and a need for bilirubin level treatment based on butane curve (case group entry criteria). On the other hand, all the neonates with ABO or Rh set up, weight loss more than 10%, hypothyroidism, hypothermia, cephalohematoma, hypoglycemia, asphyxia, G6PD deficiency, birth weight less than 2500 gr, evidence of hemolytic anemia or infection, history of blood product injection, and history of gestational diabetes in the mother were excluded from the study. A researcher-made checklist was used to collect demographic and clinical information of newborns in both groups; subsequently, 1cc of blood was collected from each neonate in the EDTA tube for further genetic testing.

DNA extraction

Total genomic DNA was extracted from EDTA-anticoagulated blood samples by a standard technique using a DNA Extraction kit (General Biosystems, Seoul, Korea) according to the manufacturer's protocol. DNA quality assessment was performed by agarose gel electrophoresis. NanoDrop 1000 was used to quantify the DNA concentration.

In order to genotype the 388A>G variant, polymerase chain reaction-restriction fragment polymorphism (PCR-RFLP) was carried out using the forward (5-ATAATGGTGCAAATAAAGGGG-3) and reverse (5-ACTATCTCAGGTGATGCTCTA-3) primers covering the specific site for restriction enzyme TaqI. The PCR-amplification was performed with an Astec Gradient thermocycler (Tokyo, Japan) in a final volume of 25 µl containing 20 ng of genomic DNA under the following conditions; an initial denaturation at 94°C for 2 min, followed by 35 cycles of denaturation at 94°C for 45 sec, annealing at 52°C for 45 sec, extension at 72°C for 45 sec, and a final extension at 72°C for 7 min. The resulting PCR products were checked on 2% agarose gel and then digested with TaqI at 65°C for 3 h. If allele A was present, the product was broken down into 151 and 63 bp, while the product was broken into 128, 63, and 23 bp at the presence of allele G.

Regarding the other variant 521T>C, genotyping was performed through RFLP using TTGTCAAAGTTTGCAAAGTG and GAAGCATATTA CCCATGAGC as forward and reverse primers covering the specific site for restriction enzyme Hha1. The PCR was performed with the same aforementioned thermal conditions, and the

resulting PCR products were checked on 2% agarose gel and then digested with Hha1 at 37°C for 18 h. The wild T allele lacked the restriction site (209 bp); nonetheless, the PCR product containing the rare C allele was cleaved to a 188-bp and a 21 bp fragment.

Statistical analysis

The Chi-square test was used to assess genotypic and allelic frequencies, as well as the relationship between the genetic polymorphisms and the risk of neonatal hyperbilirubinemia. Differences between the quantitative variables were evaluated by the Student t-test (between case and control groups). Binomial logistic regression analysis was applied to determine the odds ratios (ORs) with 95% confidence interval (CI), both in crude and adjusted gestational age, birth weight, and gender by making a comparison between each genotype (heterozygous, homozygous) and the wild type. The pair-wise D and r2 values for linkage disequilibrium (LD), as well as haplotype frequencies for two genetic variants, were estimated using online cubeX software (24). The data were analyzed in SPSS software (version 22.0), and a p-value of less than 0.05 was considered statistically significant.

Results

The baseline characteristics of 100 cases and 100 controls are summarized in Table 1. No significant difference was observed in gender distribution (P=0.951), gestational age (P=0.311), birth weight (P=0.572), and types of feeding (P=0.223) between the two study groups. The difference in vaginal delivery between the case (80%) and control (52%) groups was significant (P=0.001). As expected, the total serum bilirubin level (TBL) was significantly higher in the case group (18.31±6.17 vs 9.04±3.66) (P<0.001).

Allele frequency and genotype distribution

Genotype distribution, allele frequency, and association of 388A/G and 521T/C variants with NHB are presented in Table 2. Genotype frequencies of the two variants were in accordance with Hardy-Weinberg equilibrium both in the total sample and based on each group separately (P>0.05). Regarding the 388A/G polymorphism, no significant difference was detected for AA, AG, and GG genotypes between the cases and controls (P=0.557). The crude odds ratios for the hyperbilirubinemia in subjects with AG or GG genotypes indicated no evidence for any increased or decreased risk, compared to the AA genotype as the reference group (OR=1.18: 95% CI (0.65-2.15), P=0.596 and OR=1.73: 95% CI (0.63-4.77), P=0.286, respectively). Similar results were obtained after adjusting for gestational age, birth weight, and gender (OR=1.34: 95% CI (0.68-2.60), P=0.395 and OR=1.91: 95% CI (0.62-5.91), P=0.26, respectively). Moreover, the difference in allelic frequencies A and G between the two groups was not significant (OR=0.83: 95% CI (0.55-1.24); P=0.353).

In the case of the 521T>C variant, no significant difference was noted for genotype and allelic distributions between the cases and control subjects (P=0.169 and P=0.762, respectively). The crude odds ratios were also determined for the risk of hyperbilirubinemia in subjects carrying the CT and CC genotypes, as well as rare allele C, and the results failed to reveal any evidence of a significant increase or decrease in the risk of hyperbilirubinemia (OR=1.60: 95% CI (0.79-3.24), P=0.192; OR=0.27: 95% CI (0.03-2.44), P=0.242; and OR=0.91: 95% CI (0.50-1.65), P=0.762). Adjustment for gender, birth weight, and gestational age did not change the results (OR=1.27: 95% CI (0.56-2.87), P=0.572 and OR=0.38: 95% CI (0.04-3.89, respectively), P=0.413) (Table 2).

Table 1. Characteristics of the infants with and without hyperbilirubinemia

Characteristics	Case (n = 100)	Control (n = 100)	*P* value
M/F	55/45	53/47	0.951*
Gestational Age (weeks)	38.41 ± 4.03	38.99 ± 1.09	0.311**
Birth Weight (gr)	2964.20 ± 441.30	3099.70 ± 469.10	0.572**
STB (mg/dl)	18.31 ± 6.17	9.04 ± 3.66	0.001**
Delivery Type	-	-	-
Vaginal	79 (79)	52 (52.0)	< 0.001*
Cesarean	21 (21)	48 (48.0)	
Types of feeding	-	-	-
Exclusive breastfeeding	80 (80)	72 (72)	
Exclusive formula feeding	2 (2)	0 (0)	0.223***
Mixed feeding	18 (18.9)	28 (28)	

M/F, male/female; STB, Serum total bilirubin; Values were expressed as mean ±SD. P-value Cases vs. Controls.
* *P* of X^2 test, ** ^{b}*P* of student T test, *** *P* of Fisher exact test.

Table 2. Genotype distribution and allele frequencies of the OATP2 polymorphisms in infants with and without hyperbilirubinemia

	Cases (n = 100)	Controls (n = 100)	Adjusted OR[a] (95% CI)	[a]*P*
388A>G				
Genotype, n (%)				
AA	37 (37)	32 (32)	1.00	-
AG	55 (55)	56 (56)	1.34 (0.68-2.60)	0.395
GG	8 (8)	12 (12)	1.91 (0.62-5.91)	0.260
		[b]*P* = 0.103		
A allele	129 (64)	120 (60)	1.00	
G allele	71 (36)	80 (4)	1.55 (0.93-3.33)	0.353
		[b]*P* = 0.353		
521T>C				
Genotype, n (%)				
TT	80 (80)	75 (75)	1.00	
CT	16 (16)	24 (24)	1.27 (0.56-2.87)	0.572
CC	4 (4.0)	1 (1)	0.38 (0.04-3.89)	0.413
		[b]*P* = 0.169		
T allele	176 (88)	174 (87)	1.00	-
C allele	24 (12)	26 (13)	0.91 (0.50-1.65)	0.762
	[b]*P* = 0.762			

OR, odds ratio; CI, confidence interval. P> 0.05: Not significant
[a]*P* of Logistic regression models adjusted for gestational age, gender, and birth weight
[b]*P* of X^2 test related to allelic and genotypic differences between cases and controls

Table 3. Distribution and comparison of the frequency of diplotypes and haplotypes

		The whole population (n=200)	Case group (n=100)	Control group (n=100)	OR* (95% CI)	P value
Diplotypes	A/A-T/T	64 (32)	34 (34)	30 (30)	---	0.734
	A/A-X/C	5 (2.50)	3 (3)	2 (2)	---	
	X/G-T/T	91 (45.50)	46 (46)	45 (45)	---	
	X/G-X/C	40 (20)	17 (17)	23 (23)	---	
Haplotypes	A-T	0.60	0.62	0.59	1	---
	G-T	0.27	0.26	0.28	1.21 (0.72-2.03)	0.470
	G-C	0.10	0.09	0.12	1.31 (0.67-2.53)	0.430
	A-C	0.02	0.03	0.02	0.69 (0.15-3.16)	0.630
Disequilibrium						
	D'	0.73	0.65	0.81		
	r^2	0.12	0.10	0.15		

Diplotype and haplotype analysis

In order to assess the combined effect of the two polymorphisms on the risk of hyperbilirubinemia, neonates in both case and control groups were stratified according to the combination of the two genotypes of study SNPs (AA-TT, AA-XC, XG-TT, and XG-XC). The results illustrated no significant difference in diplotype distribution between the two groups (P=0.734; Table 3).

The haplotype frequencies and the degree of linkage disequilibrium by D' and r2 were also compared between case and control groups (Table 3). The two polymorphisms were in strong linkage disequilibrium (D'=0.65, r2=0.10 in cases and D'=0.81, r2=0.15 in controls). There were four possible haplotypes, including A-T, G-T, G-C, and A-C, with an estimated frequency above 1% in both groups. No significant difference was detected between the two study groups in haplotype distribution.

Discussion

The association between neonatal hyperbilirubinemia and OATP2 genetic polymorphisms is not fully understood. The results of previously conducted studies have pointed out that 388A>G and 521T>C polymorphisms related to the OATP2 gene may lead to neonatal hyperbilirubinemia by preventing bilirubin uptake in hepatocytes (25). The role of UGT1A1 and OATP2 gene polymorphisms in unconjugated hyperbilirubinemia has already been demonstrated (19). The current study sought to discuss the correlation between two OATP2 gene variants (388A>G and 521T>C) and the risk of hyperbilirubinemia in Iranian neonates.

The results of this study indicated no statistically significant differences between the two 388A>G and 521T>C polymorphisms in neonates with or without hyperbilirubinemia. Previous studies have pointed to the association of genotype and allele frequencies of OATP2 variants with race (25). In the same

context, a similar study in Indonesia showed no relationship between the OATP2 388A>G variant and hyperbilirubinemia (26). The OATP2 gene variants at the nucleotide 388A>G, c.521T>C, c.571T>C, and c.597C>T presented a non-significant association with higher bilirubin levels among neonates with severe hyperbilirubinemia in Malaysian, Chinese, and Thai neonates (17, 27). Nonetheless, neonates with the OATP2 388A>G and UGT1A1 nt211 (a high-risk factor of hyperbilirubinemia) variants were found in Taiwanese and Indian populations (19, 28). In contrast with the findings of the present research, Liu et al. reported that OATP2 388A>G was significantly higher in neonates with hyperbilirubinemia in Chinese neonates; however, no significant differences were found for OATP2 521T>C variant (29). Accordingly, 388A>G and UGT1A1 G71R gene mutations, along with G6PD deficiency in the Guangxi population, were defined as risk factors for neonatal hyperbilirubinemia (30). Moreover, the discrepancy in various studies can be ascribed to differences in sample size and ethnicity.

In addition, diplotype and haplotype analysis of the two studied polymorphisms showed no significant effect on the risk of bilirubinemia, indicating no interaction and synergistic effect for the combination of these two polymorphisms. This is in contrast with a previous study on an Indian population, suggesting that the risk and severity of hyperbilirubinemia were significantly associated with the frequency of the mutant haplotype (19).

All things considered, the previous studies yielded contradictory results considering these two polymorphisms (31). One of the reasons for this difference can be the varied linkage disequilibrium (D') between the two variants resulting from race/ethnicity variations in different populations (32). Other OATP2 polymorphisms, more candidate genes, and environmental risk factors should be investigated in further studies to elucidate the precise etiology of the disease. It is also important to analyze their association with prognosis and severity of the disease.

Conclusion

As evidenced by the results of the present study, the OATP2 gene 388A>G and 521T>C variants showed no significant association with the risk of neonatal hyperbilirubinemia in an Iranian population of neonates. Further studies in larger and diverse ethnic populations are needed to support the obtained results.

Acknowledgments

This study was supported by research project No.951151 as a thesis in neonatology residency at Mashhad University of Medical Sciences. We thank the Department of Pediatrics and the Clinical Research Development Unit, Ghaem Hospital, for their assistance in this research.

Conflicts of interest

The authors declare no conflict of interest regarding the publication of this paper.

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