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POLYMORPHISMS OF CYTOKINE GENES AND RISK OF EARLY NEONATAL SEPSIS IN PREMATURITY

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Abstract
The study of the relationship between gene polymorphisms encoding cytokine production will make it possible to predict the risk of pathology development, as well as the nature and severity of its course. *Objective:* To study the significance of cytokine gene polymorphisms IL-6, IL-10, and TNF-α in premature newborns in the development of early neonatal sepsis. *Materials and Methods:* A total of 148 mothers and their newborns were examined and divided into the main and control groups. The main group consisted of 82 premature newborns with early neonatal sepsis. The control group consisted of 66 practically healthy newborns. *Results:* It was found that IL-6 -174C/G polymorphism, genotype GG and allele G play a significant predisposing role in the group of premature infants with early sepsis. Allele C and genotypes CC, CG of IL-6 -174C/G were shown to have a protective effect. The TNF -308(G/A) polymorphism, genotype GA, may have a predisposing significance for the development of early sepsis in premature infants. No contribution of the IL-10 G-1082A (rs1800896) polymorphism to the development of the studied pathology in this sample was found.

Keywords: Newborns, neonatal sepsis, cytokines, gene polymorphism.

1. INTRODUCTION

Neonatal sepsis remains one of the leading causes of morbidity and mortality among newborns worldwide. According to WHO data, sepsis accounts for 15–20% of infant deaths [15]. Premature infants represent a particularly high-risk group, as immune system immaturity, low birth weight, and a high frequency of maternal obstetric complications contribute to the rapid development of generalized infection and severe complications [2,6].

Early neonatal sepsis, which develops within the first 72 hours of life, represents the most severe form of infectious-inflammatory pathology in newborns. In premature infants, it is characterized by a fulminant course, atypical clinical presentation, and high mortality [3,10]. The difficulties of early diagnosis are associated with the absence of specific symptoms and the limited informativeness of standard laboratory markers. Despite the introduction of indicators such as C-reactive protein, procalcitonin, and presepsin into clinical practice, there is still a need for more sensitive and specific prognostic criteria [1,4,7].

Modern research convincingly demonstrates that cytokines — regulators of innate and adaptive immune responses — play a key role in the pathogenesis of neonatal sepsis. Primary pro-inflammatory mediators, such as tumor necrosis factor alpha (TNF-α) and interleukin-1β (IL-1β), trigger a cascade of inflammatory reactions by stimulating the production of secondary cytokines, including IL-6 and IL-10 [7,11]. The imbalance between pro- and anti-inflammatory cytokines determines the severity of sepsis and its outcome. In premature infants, hyperproduction of IL-10, accompanied by a reduction of the anti-infective barrier, often leads to adverse outcomes [8].

In recent years, increasing attention has been paid to the genetic aspects of susceptibility to sepsis. It has been demonstrated that variability in cytokine production in newborns is largely determined by gene polymorphisms regulating their expression [5,9]. The most clinically significant are polymorphisms in the promoter regions of IL-6 (rs1800795), TNF-α (-308G/A), and IL-10 genes. According to some studies, carriage of the GG genotype for IL-6 (rs1800795) is associated with an increased risk of early sepsis, whereas the heterozygous CG variant has a protective effect [13]. Similarly, the A allele and G/A genotype of TNF-α (-308) are linked to susceptibility to severe sepsis, while the G allele and GG genotype have a protective effect [12].

Thus, the study of clinical and immunogenetic features of early neonatal sepsis in premature infants is highly relevant. It not only clarifies the pathogenetic mechanisms of the disease but also contributes to the development of reliable prognostic criteria for severity and outcomes, which is of practical importance for timely diagnosis, optimal therapy selection, and reducing adverse consequences [14].

Objective of the Study: To investigate the significance of cytokine gene polymorphisms IL-6, IL-10, and TNF-α in premature newborns of the Uzbek population in the development of early neonatal sepsis.

2. MATERIALS AND METHODS

Genetic studies were conducted at the Institute of Immunology and Human Genomics of the Academy of Sciences of the Republic of Uzbekistan.

A total of 148 mothers and their newborns were examined and divided into main and control groups. The main group consisted of 82 premature newborns with early neonatal sepsis. The control group included 66 practically healthy newborns born to mothers with uncomplicated pregnancies, with normal Apgar scores at birth, without intrauterine hypoxia, and with a physiological course of the early adaptation period.

Inclusion criteria: premature newborns with a confirmed diagnosis of early neonatal sepsis, with clinical manifestation of systemic infection occurring within the first 48–72 hours of life.

Exclusion criteria: genetic disorders and metabolic diseases, as well as the presence of isolated or multiple congenital malformations.

When establishing the diagnosis, maternal history, urogenital tract infections, prolonged rupture of membranes (>18 h), age 0–7 days, gestational age, presence of one or more foci of infection, at least two clinical signs of neonatal sepsis, at least two laboratory criteria, organ dysfunction, and positive blood culture results were taken into account. The diagnosis was established according to ICD-10, code P36 – Bacterial sepsis of the newborn.

Clinical studies were carried out in the neonatal pathology departments of the 5th City Children's Hospital. The newborns' condition was assessed using the Apgar score at 1 and 5 minutes after birth. Morphofunctional and neuromuscular maturity were evaluated using the Ballard scale. Physical development was assessed through anthropometric measurements.

Genetic studies were carried out at the Institute of Immunology and Human Genomics of the Academy of Sciences of Uzbekistan. Venous blood from the cubital vein was used as material for DNA extraction. Genomic DNA was isolated using a two-stage blood cell lysis method. The subsequent purification of leukocyte lysates was based on the alcohol-salt treatment method described by S. Miller et al. (1988) and modified by the Stanford University laboratory.

Genotyping of polymorphic regions of immune response genes was performed by polymerase chain reaction (PCR) with allele-specific primers (NPF "Litekh," Russia) and electrophoretic detection of reaction products in agarose gel. Three SNPs were tested: IL-6 174 C/G (rs1800795), IL-10 (G-1082A), and TNF (G-308A). All tested SNPs were previously validated and have a minor allele frequency of 1% or higher (NCBI dbSNP database, http://www.ncbi.nlm.nih.gov/projects/SNP/index.html).

Amplification products were identified and compared with size markers under UV light (310 nm) after electrophoresis for 15 minutes at 300 V (migration distance 3–4 cm), followed by ethidium bromide staining.

The distribution of genotypes in the studied polymorphic loci was analyzed using logistic regression and tested for Hardy–Weinberg equilibrium using Fisher's exact test. Matching by sex and age was taken into account for both patients and controls. Differences were considered statistically significant at $p < 0.05$.

3. RESULTS AND DISCUSSION

We analyzed the distribution of allele and genotype frequencies of IL-6, IL-10, and TNFα in premature newborns with early sepsis.

The study of IL-6 -174C/G genotype frequencies showed that the GG genotype was significantly more frequent in the group of premature infants with early sepsis (67.74%) compared to the control group (34.85%), with OR = 3.926; $\chi^2 = 9.208$ ($p = 0.00241$); 95% CI: $1.584 < 3.926 < 9.729$.

The frequency of the G allele was also significantly higher in the group of affected premature infants (79.03%) compared to controls (59.09%), with OR = 2.609; $\chi^2 = 7.42$ ($p = 0.006451$); 95% CI: $1.292 < 2.609 < 5.271$.

The CG genotype had a protective effect and was more frequently observed in the control group (48.48%) compared to the group of premature infants with sepsis (22.58%), with OR = 0.31; $\chi^2 = 5.887$ ($p = 0.015249$); 95% CI: $0.117 < 0.31 < 0.818$.

Thus, the obtained data indicate a significant contribution of the GG genotype of IL-6 174 C/G (rs1800795) to the development of this pathology (Table 1).

Table 1. Distribution of IL-6 174 C/G (rs1800795) Genotypes in Premature Newborns with Early Sepsis

Genotype	Patients, n=31(%)	Control, n=66 (%)	χ2 (p)	OR (95% CI)
C	13 (20,97)	54 (40,91)	7.42 (0.006451)	0.383 (0.19 -0.774)
G	49 (79,03)	78 (59,09)		2.609 (1.292 -5.271)
CC	3 (9,68)	11 (16,67)	0.834 (0.361027)	0.536 (0.138 -2.077)
CG	7 (22,58)	32 (48,48)	5.887 (0.015249)	0.31 (0.117 -0.818)
GG	21 (67,74)	23 (34,85)	9.208 (0.00241)	3.926 (1.584 -9.729)

Note: χ^2 – Pearson's chi-square value; OR – odds ratio.

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At the next stage, we analyzed the frequency of alleles and genotypes of the IL-10 G-1082A (rs1800896) gene in the group of premature newborns with early sepsis (Table 2).

As shown in the table, no statistically significant differences were found in allele and genotype frequencies between the subgroup of premature newborns with early sepsis and the control group. This allows us to conclude that IL-10 G-1082A (rs1800896) does not contribute to the development of the studied pathology in this sample.

Table 2. Distribution of IL-10 G-1082A (rs1800896) Alleles and Genotypes in the Group of Premature Newborns with Early Sepsis

Genotype	Patients, n=31(%)	Control, n=66 (%)	χ2 (p)	OR (95% CI)
G	37 (59,68)	88 (66,67)	0.899 (0.342989)	0.74 (0.397 -1.38)
A	25 (40,32)	44 (33,33)		1.351 (0.725 -2.52)
GG	7 (22,58)	23 (34,85)	1.486 (0.222839)	0.545 (0.204 -1.456)
GA	23 (74,19)	42 (63,64)	1.063 (0.302433)	1.643 (0.637 -4.24)
AA	1 (3,23)	1 (1,52)	0.306 (0.580351)	2.167 (0.131-35.822)

Note: χ^2 – Pearson's chi-square value; OR – odds ratio.

Next, we analyzed the allelic variants and genotypes of TNFα -308G/A in premature newborns with early sepsis (Table 3). According to the obtained data, differences were observed in the distribution of the GG genotype between the group of premature newborns with early sepsis (67.74%) and the control group (84.85%) (OR = 0.375; 95% CI: 0.137 < 0.375 < 1.029; χ^2 = 3.771; p = 0.052142).

When analyzing the heterozygous GA genotype, an opposite pattern was revealed: its frequency in premature infants with sepsis was twice as high (32.26%) as in the control group (15.15%) (OR = 2.667; 95% CI: 0.971 < 2.667 < 7.321; χ^2 = 3.771; p = 0.052142).However, it should be noted that in this group the indicators did not reach true statistical significance. With an increased sample size, these indicators may potentially achieve statistically significant values.

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Table 3. Distribution of TNFα -308G/A (rs1800629) Allele and Genotype Frequencies in the Group of Premature Newborns with Early Sepsis

SNP	Group	Allele	Allele frequency, %	χ2 (p)	OR (95% CI)	Gen otype	Genotype frequency, %	χ2 (p)	OR (95% CI)
TNFA rs1800629	Study group n=31	G	83,87	3.338 (0.067707)	0.426 (0.167-1.085)	GG	67,74	3.771 (0.052142)	0.375 (0.137 - 1.029)
		A	16,13		2.346 (0.921-5.974	GA	32,26		2.667 (0.971 - 7.321)
						AA			
	Control n=66	G	92,42			GG	84,85		
		A	7,58			GA	15,15		
						AA			

Note: χ^2 – Pearson's chi-square value; OR – odds ratio.

4. CONCLUSIONS

Thus, the obtained data indicate that the IL-6 -174C/G polymorphism, specifically the GG genotype and G allele, play a significant predisposing role in the group of premature infants with early sepsis. The C allele and CC and CG genotypes of IL-6 -174C/G have a protective effect. Our results also demonstrate that the TNF -308(G/A) polymorphism, genotype GA, may have a predisposing significance for the development of early sepsis in premature infants.

At the same time, we identified no contribution of the IL-10 G-1082A (rs1800896) polymorphism to the development of the studied pathology in this sample. These findings highlight the need for further research.

The identified genetic markers of susceptibility and resistance of the studied cytokine polymorphisms to the development of early sepsis in premature newborns of the Uzbek population may be used as prognostic criteria for predicting the development of this disease.

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