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EVALUATION OF THE RELATIONSHIP BETWEEN CYTOKINE GENES AND HYPERLEUKOCYTOSIS IN ACUTE LEUKEMIA

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Abstract

Objective. To study the relationship between the polymorphism of the gene IL17F (rs763780) and the development of hyperleukocytosis in acute leukemia.

Methods. The material for clinical and laboratory studies in the work were patients with AL (n=102; ALL – 70 and AML - 32) who were admitted to the republican specialized scientific and practical medical Center of Hematology (RSSPMCH, Tashkent) from 2019 to 2023. Patients with AL were aged from 18 to 74 years, while the median age was 37.0±1.5 years. The diagnosis was established on the basis of diagnostic standards, taking into account clinical and laboratory data.

The research methods included, in addition to clinical and laboratory (general blood test, myelogram), molecular biological research methods (detection of polymorphic gene IL17F (rs763780) by PCR in RT mode). The results were statistically processed using the PC application package "OpenEpi 2009, Version 2.3".

Conclusions. Weakened loci of the polymorphic gene IL17F (rs763780) (allele (Arg) - $\chi 2=10.4$; P=0.01 and genotype (His/Arg) - $\chi 2=4.7$; P=0.05) are significantly associated with hyperleukocytosis (>30 x 109/l) in AL.

Keywords: Hyperleukocytosis, polymorphism, cytokines, risk of development.

Introduction

Hyperleukocytosis (HL) is most common in patients with acute lymphoblastic leukemia (ALL) and somewhat less common in patients with acute myeloid leukemia (AML) [12]. The criteria suggest the occurrence of HL complications with a leukocyte level in peripheral blood of more than 30,000/mm ^{3}, the literature describes cases of HL symptoms with a leukocyte count of up to 50×10^3 [8,10].

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The molecular processes leading to hyperleukocytosis have not yet been fully identified. Meanwhile, blast cells are known to secrete inflammatory cytokines such as interleukin-17F, which increase the expression of selectin family members in endothelial cells [2,3,14]. These molecules affect not only the migration of stem cells (LSCs) in leukemia, but also their survival and resistance to chemotherapy [1,2,3,13].

At the same time, it is reported that hyperleukocytosis is associated with a poor prognosis of de novo AL [5]. In particular, a number of studies have shown that single nucleotide polymorphisms are significantly associated with the number of leukocytes [6,7,11]. In addition, leukocyte overload leads to various types of clinical manifestations, tumor lysis syndrome and thrombosis, as well as intracranial bleeding, which can lead to early death before the start of induction chemotherapy [4,9].

Purpose

To study the relationship between IL17F (rs763780) gene polymorphism and the development of hyperleukocytosis in acute leukemia.

Methods

The material for clinical and laboratory studies in the work were patients with AL (n=102; ALL - 70 and AML - 32) who were admitted to the republican specialized scientific and practical medical Center of Hematology (RSSPMCH, Tashkent) from 2019 to 2023. Patients with AL were aged from 18 to 74 years, while the median age was 37.0±1.5 years. The diagnosis was established on the basis of diagnostic standards, taking into account clinical and laboratory data.

Depending on the level of leukocytosis, the 1st combined group of patients was divided into two subgroups: 1a (n=62) - patients with leukocytosis <30 x 10^9/l and 1b (n= 40) - patients with leukocytosis >30 x 10^9/l.

The research methods included, in addition to clinical and laboratory (general blood test, myelogram), molecular biological research methods (detection of the polymorphic gene IL17F (rs763780) by PCR in RT mode using test systems from “Litex” Russia on a programmable thermal cycler Applied Biosystems 2720, USA; RotorGeneQ, QUAGEN Germany and Corbett Research - CG1-96, QUAGEN Germany. The results were statistically processed using the PC application package “OpenEpi 2009, Version 2.3”.

Results

To study the role of the genetic marker IL 17F (rs763780) in increasing the risk of hyperleukocytosis (>30 x 10^9/l) between groups of patients with AL, the distribution of unfavorable and favorable loci was analyzed. In particular, according to the studied gene, among healthy people (n=95), the frequencies of (His) and (Arg) alleles were found to be equal to 94.7% and 5.3%, respectively. In the same group of examined patients, only two variants of genotypes were found: the main (His/His) and the heterozygote (His/Arg), which occurred with a frequency of 89.5% and 10.5%, respectively. The mutant form of the (Arg/Arg) genotype was found with a frequency of 5.0% among patients with leukocytosis (>30 x 10^9/l), whereas among healthy and among patients with leukocytosis (<30 x 10^9/l) in no case was this genotype detected (see Table 1).

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Table 1 Differences in polymorphic loci of the IL 17F (His161Arg) gene between the studied groups

genetic polymorphism	allele/ genotype	AL with leukocytosis (<30 x 10^9/l), (abs/%)	control group, (abs/%)	reliability
IL17F (His161Arg)	His	118/95,2	180/94,7	χ^2=0,0; P=0,9; OR=1,1; 95%CI=0,39 - 3,09
	Arg	6/4,8	10/5,3	χ^2=0,0; P=0,9; OR=0,9; 95%CI=0,32 - 2,58
	His/His	56/90,3	85/89,5	χ^2=0,0; P=0,9; OR=1,1; 95%CI=0,38 - 3,19
	His/Arg	6/9,7	10/10,5	χ^2=0,0; P=0,9; OR=0,9; 95%CI=0,31 - 2,65
	allele/ genotype	AL with leukocytosis (>30 x 10^9/l), (abs/%)	control group, (abs/%)	reliability
	His	66/82,5	180/94,7	χ^2=10,4; P=0,01; OR=0,3; 95%CI=0,12 - 0,59
	Arg	14/17,5	10/5,3	χ^2=10,4; P=0,01; OR=3,8; 95%CI=1,69 - 8,62
	His/His	28/70,0	85/89,5	χ^2=7,8; P=0,01; OR=0,3; 95%CI=0,11 - 0,68
	His/Arg	10/25,0	10/10,5	χ^2=4,7; P=0,05; OR=2,8; 95%CI=1,1 - 7,28
	allele/ genotype	AL with leukocytosis (<30 x 10^9/l), (abs/%)	AL with leukocytosis (>30 x 10^9/l), (abs/%)	reliability
	His	118/95,2	66/82,5	χ^2=8,8; P=0,01; OR=4,2; 95%CI=1,62 - 10,71
	Arg	6/4,8	14/17,5	χ^2=8,8; P=0,01; OR=0,2; 95%CI=0,09 - 0,62
	His/His	56/90,3	28/70,0	χ^2=6,9; P=0,01; OR=4,0; 95%CI=1,42 - 11,25
	His/Arg	6/9,7	10/25,0	χ^2=4,3; P=0,05; OR=0,3; 95%CI=0,11 - 0,94

Among group 1 a patient with leukocytosis <30 x 10^9/l (n=62), the cases of observation of the main and attenuated (His) and (Arg) alleles were 95.2% and 4.8%. Meanwhile, the frequencies of the main (Arg/Arg) and heterozygous (Arg/Pro) genotype variants were 90.3% and 9.7%.

Next, we studied the distribution of polymorphic loci of the gene IL 17F (rs763780) among group 1b patients with leukocytosis levels (>30 x 10^9/l), (n=62).

Analyzing the results of the distribution of polymorphic loci of the gene IL17F (rs763780) in group 1b with a leukocytosis level (>30 x 10^9/l), (n=40), compared with healthy ones, a decrease in the frequency of the (His) allele to 82.5% and an increase in the frequency of the (Arg) allele to 17.5% were revealed. At the same time, in group 1b, there was a decrease in the frequency of the main genotype of (His/His) to 70.0% and an increase in the frequency of the heterozygote of (His/Arg) to 25.0%.

A noticeable increase in the frequencies of the attenuated (Arg) allele and the heterozygous (His/Arg) genotype in the group of patients with leukocytosis levels (>30 x 10^9/l) most likely indicates their possible participation in increasing the risk of hyperleukocytosis.

The frequencies of (His) and (Arg) alleles between 1a and 1b in the patient group were 95.2%, 82.5% and 4.8%, 17.5%, respectively, while the main genotype of (His/His) and the heterozygote of (His/Arg) were determined in 90.3%, 70.0% and 9.7%, 25.0% cases, respectively (Table 1).

Thus, assessing the distribution of polymorphic loci of the gene IL17F (rs763780) among patients with leukocytosis levels (>30 x 10^9/l) and healthy, we determined the natural highest carrier of the attenuated allele (Arg) and heterozygous genotype (His/Arg) with minimal carrier of the main allele (His) and genotype (His/His). On the contrary, in the group of patients with leukocytosis levels (<30 x 10^9/l), there was an insignificant increase in the frequencies of the main allele (His)

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and genotype (His/His), while reducing the carriage of the weakened allele (Arg) and heterozygous genotype (His/Arg), as well as such changes were observed in the comparison group of patients with a leukocytosis level (>30 x 10^9/l). Based on the assessment of the distribution of polymorphic loci of the gene IL17F (rs763780), their possible role in the risk of hyperleukocytosis is obvious. Meanwhile, to confirm this assumption, it is necessary to conduct a more detailed mathematical analysis to determine the significance of differences in the carrier of alleles and genotypes according to the genetic polymorphism IL17F (rs763780) observed between groups of patients and healthy.

Assessing the degree of differences between polymorphic loci of the gene IL17F (rs763780) in relation to those in the healthy group, we found in Group 1b of patients with leukocytosis levels (>30 x 10^9/l) the presence of very pronounced differences in the carrier of a weakened allele (Arg) and a heterozygous genotype (His/Arg) (see Table 1).

In particular, in group 1b of patients with leukocytosis levels (>30 x 10^9/l), compared with healthy patients, the (Arg) allele increased statistically significantly by 3.8 times (17.5% vs. 5.3%; $\chi2$=10.4; P=0.01; OR=3.8; 95%CI: 1.69-8.62), and the heterozygous genotype of (His/Arg) was also statistically significantly higher by 2.8 times (25.0% vs. 10.5%; $\chi2$=4.7; P=0.05; OR=2.8; 95%CI: 1.1-7.28).

Consequently, the statistically significant differences found prove the contribution of the attenuated allele (Arg) and the heterozygous genotype (His/Arg) according to the genetic polymorphism IL17F (rs763780) to an increased risk of hyperleukocytosis by 3.8 ($\chi2$=10.4; P=0.01) and 2.8 ($\chi2$=4.7; P=0.05) times, respectively.

In comparison with healthy patients, assessing the nature of differences in the distribution of polymorphic loci of the gene IL17F (rs763780) in group 1a of patients with leukocytosis (<30 x 10^9/l), no statistically significant differences in the frequencies of the attenuated (Arg) allele were revealed (4.8% vs. 5.3%; $\chi2$<3.84; P=0.9; OR=0.9; 95%CI: 0.32-2.58) and (His/Arg) heterozygous genotype (9.7% vs. 10.5%; $\chi2$<3.84; P=0.9; OR=0.9; 95%CI: 0.31-2.65) due to their almost equal values.

Thus, the results of a comparative assessment in the distribution of polymorphic loci of the gene IL17F (rs763780) between groups of patients with leukocytosis levels (<30 x 10^9/l) and healthy ones are not considered as genetic predictors that increase the risk of hyperleukocytosis.

Analyzing the nature of differences in the distribution of polymorphic loci of the gene IL17F (rs763780) between groups of patients with leukocytosis levels (<30 x 10^9/l) and (>30 x 10^9/l), we found insignificant differences in the frequencies of the attenuated (Arg) allele (4.8% vs. 17.5%; $\chi2$=8.8; P=0.01; OR=0.2; 95%CI: 0.09-0.62) and (His/Arg) heterozygous genotype (9.7% vs. 25.0%; $\chi2$=4.3; P=0.05; OR=0.3; 95%CI: 0.11-0.94).In contrast, there were statistically significant differences in the frequencies of the main (His) allele (95.2% vs. 82.5%; $\chi2$=8.8; P=0.01; OR=4.2; 95%CI: 1.62-10.71) and (His/His) genotype (90.3% vs. 70.0%; $\chi2$=6.9; P=0.01; OR=4.0; 95%CI: 1.42-11.25) which indicate the protective effect of these loci (see Table 1).

Analyzing the results of the distribution of polymorphic loci of the gene IL17F (rs763780) between groups of patients with leukocytosis levels (>30 x 10^9/l) and healthy, it was determined that the carriage of a weakened (Arg) allele and a heterozygous (His/Arg) genotype is associated with an increased risk of hyperleukocytosis. In particular, when carrying a weakened (Arg) allele and a heterozygous (His/Arg) genotype according to the studied genetic polymorphism, the risk of hyperleukocytosis (>30 x 10^9/l) increases statistically significantly by 3.8 ($\chi2$=10.4; P=0.01) and

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2.8 (χ2=4.7; P=0.05) times, respectively. Thus, polymorphic loci of the gene IL17F (rs763780) can be considered as genetic predictors involved in the mechanisms of increased risk of hyperleukocytosis.

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