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Genetic Factors of Uterine Hyperplastic Processes.

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ABSTRACT

The article contains the study of implication of genetic factors in formation of uterus hyperplastic processes. Correlation of neutrophil-activating proteins' *IL-5 c. -746 T>C (rs2069812), IL-8 c.-352 A>T (rs4073) и IL-1a c.-949 C>T (rs1800587)* genetic polymorphisms with development of formation of uterus hyperplastic processes in women of Russia's Central Region.

Keywords: uterine hyperplastic processes, neutrophil-activating proteins, polymorphism.

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INTRODUCTION

Uterine hyperplastic processes (hyperplastic processes of endometrium, uterine leiomyoma, genital endometriosis) have leading position in the structure of total incidence of gynaecological diseases. They have common pathogenesis segments and that's why they are often observed jointly [1]. It is believed that uterine hyperplastic processes are hormone-dependent pathologies. Along with hormone induction in genesis of benign proliferative diseases, there exist processes that are responsible for transformation of normal cells. These processes include: hormone-independent proliferation, impaired apoptosis, pathological neoangiogenesis and inflammation. Recent studies have proven that cytokines are involved in realization of these processes.

Genetic factors play important role in aetiopathogenesis of uterus hyperplastic processes. A number of works has been dedicated to study of genetic bases of benign proliferative diseases [2, 3, 4]. It should be noted that obtained results vary among different investigators, and they do not give unambiguous answer regarding the role of genetic factors in pathogenesis of proliferative uterine diseases. In accordance with this, current work contains study of role of the following cytokines' genetic polymorphism: *IL-6 c.-237 C>G (rs 1800795), IL-1 β c.-598 T>C (rs 16944), IL-1α c.-949 C>T (rs 1800587), IL-4 c.-589 C>T (rs2243250), IL-10 c.-627 A>C (rs180082), IL-5 c. -746 T>C (rs 2069812), IL-8 c.-352 A>T (rs 4073)* in formation of uterine hyperplastic processes.

MATERIALS AND METHODS

Clinical and anamnestical indices have been studied in 735 women. Study results were compared to similar ones in 500 women without proliferative diseases of female genital organs. Main group and control group included Russian women who were native of Central Region of Russia and who were not relatives to each other. Patient work-up was performed on the base of gynaecology department of perinatal centre of Belgorod Regional Clinical Hospital of Saint Joasaph. Patients with uterine hyperplastic processes were provided with clinical and gynecological examination, ultrasound investigation if pelvic floor, hysteroscopy with further target diagnostic curettage and scrape hystologic study.

Typing of single nucleotide polymorphism of the following cytokines' genes was performed for patients with uterine hyperplastic processes women from control group: *IL-6 c.-237 C>G (rs 1800795), IL-1β c.-598 T>C (rs 16944), IL-1α c.-949 C>T (rs 1800587), IL-4 c.-589 C>T (rs 2243250), IL-10 c.-627 A>C (rs 180082), IL-5 c. -746 T>C (rs 2069812), IL-8 c.-352 A>T (rs 4073).*

Venous blood in the volume of 8-9 ml, taken from median cubital probanda vein, served as a material for study. Genomic DNA purification from peripheral blood was performed by standard method of phenol chloroform extraction from frozen venous blood [5]. Analysis of studied locuses was performed by method of polymerase chain reaction of DNA synthesis with the usage of oligonucleotide primers and probes [6, 7, 8]. Associations of genetic variants of studies DNA markers with formation of uterine hyperplastic processes were assessed via analysis of cross tables 2×2 with χ^2 criterion calculation with Yates continuity corrected and odds ratio (OR) with confidence interval of 95%. Analysis of roles of combinations of cytokines' genetic variants in occurrence of uterine hyperplastic processes was performed with the help of APSampler software [9].

RESULTS

Investigation of distribution of studied gene markers' genotypes showed that for all studies locuses in control group and in main group empirical distribution of genotypes corresponds to theoretically expectable value at Hardy–Weinberg equilibrium (p>0,05). (Table 1).

In the course of comparative analysis of allele frequency array and genotypes of polymorphic markers of neutrophil-activating proteins' genes among patients with uterine hyperplastic processes and patients from control group statistically significant differences by locus *IL-1α (rs 1800587)* were identified. It was stated that among the patients with uterine hyperplastic processes frequency of *T IL-1α* allele and *TT IL-1α* genotype equaled 26,50% and 7,96%, respectively, and exceed values obtained in control group (20,40%, χ^2=10,30, p=0,002, p_{cor}=0,006, OR=1,41, 95%CI 1,14 – 1,74 and 3,26%, χ^2=11,05, p=0,002, p_{cor}=0,006, OR=2,76, 95%CI

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1,47 – 5,25). Also, patients with uterine hyperplastic processes showed low frequency of genotype *CC IL-1α* (54,95%) comparing with control group 62,47%, χ^2=5,74, p=0,017, p_{cor}=0,05, OR=0,73, 95%CI 0,57 – 0,95).

Table 1: Summary information about the studied polymorphisms.

Polymorphism	Studied groups	Minor allele	MAF (%)	HWE	
				ч^2	p
IL-1α c.-949 C>T (rs1800587)	Case	*T*	26.50	1.53	>0.05
IL-1α c.-949 C>T (rs1800587)	Control	*T*	20.40	1.31	>0.05
IL-1β c.-598 T>C (rs16944)	Case	*T*	33.36	0.28	>0.05
IL-1β c.-598 T>C (rs16944)	Control	*T*	34.58	0.25	>0.05
IL-4 c.-589 C>T (rs2243250)	Case	*T*	20.60	0.01	>0.05
IL-4 c.-589 C>T (rs2243250)	Control	*T*	18.87	0.19	>0.05
IL-5 c.-746 T>C (rs2069812)	Case	*T*	26.55	0.07	>0.05
IL-5 c.-746 T>C (rs2069812)	Control	*T*	27.59	0,004	>0.05
IL-6 c.-237 C>G (rs1800795)	Case	*C*	48.18	0.01	>0.05
IL-6 c.-237 C>G (rs1800795)	Control	*C*	44.63	0.01	>0.05
IL-10 c.-627 A>C (rs180082)	Case	*A*	24.91	1.76	>0.05
IL-10 c.-627 A>C (rs180082)	Control	*A*	24.44	1.42	>0.05
IL-8 c.-352 A>T (rs4073)	Case	*A*	48.54	0.06	>0.05
IL-8 c.-352 A>T (rs4073)	Control	*A*	48.76	0.94	>0.05

Notes: MAF, minor allele frequency; Hardy – Weinberg equilibrium. P values were calculated using the χ2 test.

With the help of bioinformative approaches it was stated that individuals with proliferative uterine processes differ from control group by distribution of two various combinations of three polymorphic locuses *IL-1α c.-949 C>T (rs 1800587), IL-5 c.-746 T>C (rs 2069812), IL-8 c.-352 A>T (rs 4073)* (Table 2).

Table 2: Concentration combinations of alleles/genotypes of cytokine genes in patients with genital endometriosis and in the control group

SNP 1	SNP 2	Carriage		Fisher's p-value (Bonferroni correction, p_{cor}) Permutation test, p_{perm}	Odds ratio (95% CI)
		Case	Control		
T IL-8	*TT IL-1α*	1.60	7.22	0.0000007 (0,02) 0.000006	0.21 (0.09-0.45)
TT IL-1α	*T IL-5*	2.02	9.84	0.0000008 (0,02) 0.000006	0.18 (0.07-0.44)

It has been discovered that combination of genetic variants *TT IL-1α* with *T IL-5* and *TT IL-1α* with *T IL-8* occur in 2,02% and 1,60% of sick women, respectively, which is 4,5-4,9 times lower than that occur in control group (9,84%, p_{bonf} =0,02, p_{perm}=0,000006 and 7,22%, p_{bonf} = 0,02, p_{perm}=0,000006, respectively). When there are these combinations of polymorphic markers, pathology risk of uterine hyperplastic processes is significantly lower (OR=0,18 and OR=0,21, respectively).

CONCLUSION

As a result of performed study there have been identified genetic variants of neutrophil-activating proteins, which are associated with uterine hyperplastic processes' risk. Thus, we have discovered that development of uterine hyperplastic processes is associated with genetic variants *T IL-1α* (OR=1,41), *TT IL-1α* (OR=2,76), *CC IL-1α* (OR=0,73) and combinations of *TT IL-1α* with *T IL-5* (OR=0,18) and *TT IL-1α* with *T IL-8* (OR=0,21). Pathogenetic significance of genetic polymorphisms *IL-1α c.-949 C>T (rs 1800587), IL-5 c.-746 T>C (rs 2069812), IL-8 c.-352 A>T (rs4073)* at formation of uterine hyperplastic processes, discovered in our study, is consistent with literature data by their medico-biological effects. Genotype *TT IL-1α* is present in two combinations of genetic variants of neutrophil-activating proteins. According to literature data, this genetic variant significantly increases level of *IL-1α* [10]. Reportedly, increasing of this cytokine's level is associated with activation of endothelial cells with increasing expression of adhesive molecules, activation of neutrophiles and increased synthesis of acute-phase proteins. Besides, *IL-1* has stimulatory effect on T- and B-lymphocytes, it is able to activate synthesis of other cytokines (IL-2, -3, -4, -5, -6, -7, -8). According to literature data, IL-8 may stimulate angiogenesis by means of proliferation of endothelial and smooth muscles' cells

SUMMARY

As it can be seen from the above, genetic variants T IL-1α and TT IL-1α are risk factors with regard to development of uterine hyperplastic processes, (OR=1,41 and OR=2,76, r4espectively), and polymorphic variant *CC IL-1α* serves as a protective factor of this pathology's formation (OR=0,73). Protective meaning at formation of proliferative uterine processes belongs to combination of *TT IL-1α* genotype with *T IL-8* allele (OR=0,19) and combination *TT IL-1α* genotype with *T IL-5* allele (OR=0,18).

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