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Association of C-511 polymorphism of interleukin 1β gene with uterine adnexae inflammation in puberty age girls

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The aim of the study was to analyze the association of 511C/T polymorphism of IL-1β gene (rs16944) with specific and nonspecific salpingoophoritis in juvenile girls (12-18 years). The IL-1β 511C/T gene polymorphism was analyzed by means of polymerase chain reaction in 88 patients with salpingoophoritis and 31 healthy individuals. Among patients with nonspecific salpingoophoritis T-allele frequency dominates the CC-genotype by 4.99 times. The presence of T-allele or TT genotype of IL-1β gene increases a predisposition risk for adnexal inflammation, regardless of their specificity, in girls of pubertal age (especially at the age of 15-18) by 1.54-2.58 times [OR=2.34-4.17, OR 95% CI=1.07-12.6 p≤0.032-0.002]. C-allele and CC genotype play a protective role and show the lowest probability of adnexal inflammation, especially nonspecific salpingoophoritis [OR = 0.28-0.43, p≤0.022-0.001]. Thus, T-allele of IL-1β gene C-511T polymorphism is associated with adnexa inflammation in girls at the age of puberty.

Keyword: IL-1β gene 511C/T, salpingoophoritis, juvenile girls.

1. Introduction

General diseases of the pelvic organs in juvenile girls are one of the most important problems of obstetrics and gynecology. Very often late visit to a doctor for medical aid and late diagnostics become the cause of untimely and sometimes insufficient treatment with unpredictable consequences: menstrual disorders, relapsing exacerbations of adnexa inflammations and their complications, development of chronic pain syndrome, probable extrauterine pregnancy in future or infertility. A set of causes for the development of adnexa inflammation at the age of puberty includes both specific (infectious) and non-specific factors including genetic ones.

Certain genetic polymorphisms modify the influence of environmental factors on the body (smoking, stresses, quality and mode of diets, radiation ground, pollution of the atmosphere, water etc.), potentially playing an important role in changing gene expression and risk inherit respectively [1-5]. That is why, studying genetics of adnexa inflammation in girls at the age of puberty becomes an important social-economic

and medical value today. Genetically stipulated dysregulation of an inflammatory response in the focus of affliction can be a result of point gene mutations of IL [6, 7].

The activity of IL-1 production is coded by two separate genes: interleukin-1 alpha (IL-1α) and interleukin-1 beta (IL-1β), located in the locus of 2q14 chromosome (q13-21), in the cluster of which there is IL-1 (IL-1Ra) antagonist receptor gene [8, 9]. The function of the latter consists of antagonism of IL-1receptor and blockade of biological effects of IL-1α i IL-1β, respectively. In this way cytokine genes regulate the character of immune response and activity of inflammatory processes of the body in response to endogenic and exogenic factors. Biallele polymorphisms of IL-1β in the positions of -511, -31 та +3954 are the most studied, which are single nucleotide transitions [10, 11].

Point mutation in 511 position of IL-1β gene promoter is of certain clinical interest. Polymorphic variants of this gene are proved to be highly active concerning the production of the similar cytokine. Homo- and heterozygous carriers of the IL-1β gene mutant allele produce by four- and two-fold more of corresponding cytokine than homozygous "wild" allele carriers and associate with severe course of endometriosis [7], with severity of ulcerous diseases and efficacy of eradication therapy [12], chronic obstructive lung disease [13], high risk of renal failure [14], purulent sinusitis in children [11], etc.

As 511C/T polymorphism of IL-1β gene (id.: rs16944) plays an important role in the immune system activity and may be one of the main causes of genetically determined dysregulation of inflammatory response and possible susceptibility to antibacterial therapy. We have considered it necessary to make an analysis of 511C/T polymorphism of IL-1β gene (id.: rs16944) in the structure of salpingoophoritis in juvenile girls and to detect probability of its influence upon the development of specific or non-specific adnexa inflammation including age consideration.

Consequently, the aim of our study was to analyze associations of 511C/T polymorphism of IL-1β gene (id.: rs16944) according to specific and non-specific salpingoophoritis in girls of early (12-14 years) and late (15-18 years) juvenile age.

2. Materials and Methods

2.1 Compliance with bioethics

The study was performed in compliance with the Council of Europe Convention on Human Rights and Biomedicine and the Recommendations of the Committee on Bioethics of the Ministry of Public Health of Ukraine. Patients' Examination Cards and Patients' Informed Consent Forms were approved by the Biomedical Ethics Commission of Bukovinian State Medical University, the Ministry of Public Health of Ukraine (Chernivtsi, Ukraine). All enrolled patients were treated in the Department of Gynecology and Juvenile Gynecology of Maternity Clinical Hospital #2 (Chernivtsi, Ukraine) during 2011-2013 y.y. Genetic bench study performed in the laboratory of the Department of Medical Biology and Genetics of Bukovinian State Medical University. After screening (matching inclusion/exclusion criteria) 88 teenage girls were selected for further examination. The control group included 31 healthy teenage girls.

2.2 Inclusion / Exclusion criteria

Inclusion criteria. Juvenile age virgo girls (12-18 y.o.) with salpingoophoritis typical symptoms (primary acute salpingoophoritis or exacerbation of chronic salpingoophoritis) proved by clinical and gynecological examinations: acute pelvic pain with or without menstrual disorders or vaginal discharge, the irradiation of pain in perineal region, lumbar and sacral spine, fever, etc.; no exacerbation of chronic extragenital inflammatory diseases; no other gynecological disorders at the time of inclusion into study.

2.3 Exclusion criteria: We excluded patients younger than 12 y.o and older than 18 y.o.; treated surgically for gynecological problem in anamnesis or presenting symptoms of chronic salpingoophoritis; or presenting undercurrent factors that can cause menstrual disorders (extra tube-ovarian and extra genital organ concomitant inflammation, pregnancy, anatomical genital

anomalies, etc.); subjects with other gynecological problems; teenagers who started sexual life (non-virgo); persons with psychological disorders.

2.4 Diagnosis of Salpingo Oophoritis

Selection of patients and their distribution into groups was performed according to the classifications of Ukrainian and International Societies of Obstetrics and Gynecology (International Societies of Obstetrics & Gynecology, European Society of Gynecology) [15-17]. The diagnosis of salpingoophoritis was made on the basis of the criteria of the acting national and international recommendations [15-17].

All patients were examined comprehensively: general clinical, gynecological, laboratory and instrumental examination (ultrasound of the pelvic organs).

2.5 Genotyping of the IL-1B − 511 T>C polymorphism

Genomic DNA was extracted from peripheral blood leukocytes using the "DNA-sorb-B" test system, with primers specific to the genes' alleles [18]. Detection of -511 T>C polymorphism of IL-1β gene deletions was performed by the multiplex polymerase chain reaction (PCR) according to the manufacturer's protocol. Allele-specific primers were used in the PCR (Table 1). PCR amplification was conducted in a total volume of 25 µl containing: 200 ng of isolated DNA, 65 mM Tris-HCl pH=8.9, 0.05% Tween 20; 16 mM $(NH_4)_2SO_4$, 3.5 мМ $MgCl_2$), 0.8×SYBR Red, 0.2 mM of each dNTPs, 0.3 µM of each primer (tab. 1) and 0.5 of thermostable Taq polymerase (Applied Biosystems, USA). The amplification conditions were subjected to initial denaturation at 95 °C for 2 min; 35 cycles consisting of denaturation at 94 °C for 30 s, primer annealing at 55 °C for 30 s and DNA elongation at 72 °C for 40 s; the final DNA extension was at 72 °C for 5 min. The PCR products were digested overnight by restriction endonuclease AvaI for C-allele+ (Fermentas, Lithuania) at 37 °C. The PCR products (TT genotype - 304 bp, CC – 190 and 114 bp, CT – 304, 190 and 114 bp) were separated by horizontal electrophoresis on 3% agarose gels, stained with 4 µl of ethidium-bromide and visualized by in the presence of molecular mass ladder (100-1000 bp) using a UV transilluminatior (Nyxtechnic, USA).

Table 1: Primer sequences for IL-1β -511 (C/T) gene SNP and size of fragments

SNP locus	Primers	Primer sequences (5'-3')	Size of fragments, bp
IL1β 2q14.2	Forward	5′-TGG CAT TGA TCT GGT TCA TC -3′	Allele C: 190 bp, 114 bp Allele T: 304 bp
	Reverse	5′- GTT TAG GAA TCT TCC CAC TT –3	

bp – base pair

2.6 Statistical analysis

Statistical analysis was performed using Statistica 7.0 (StatSoft Inc, USA) software. P value and odds ratio (OR), with 95% confidence interval (CI) using a chi-square test were determined for the calculated frequencies of each allele and genotypes. Risk ratios (RR) were estimated by OR. Adjusted OR and 95% CI were estimated for association between age, specific/non-specific adnexa inflammation and genetic polymorphism. P values <0.05 were considered statistically significant.

3. Results and Discussions

88 juvenile girls with salpingoophoritis were screened. Among the patients there were 59.1% (52) – with specific salpingoophoritis, 40.9% (36) – with non-specific adnexal inflammation; 34.1% (30) girls of early juvenile age – 12-14 years and 65.9% (58) girls of late juvenile age – 15-18 years. In the majority of the examined patients

(79.5%) adnexal inflammation was diagnosed for the first time: in girls of 12-14 years – in 100% cases, in girls of 15-18 years – in 69.0% (40) cases respectively. The reference group included healthy juvenile girls (n=31) of the following age: 12-14 years – 32.3% (10) subjects, 15-18 years – 67.7% (21) individuals, respectively (p>0.05).

Distribution of 511C/T polymorphism of IL-1β gene depending on the specificity of inflammatory processes of the adnexa and the age of the examined patients are presented in the Table 2. A relative frequency of the analyzed genotypes in individuals of 12-14 and 15-18 years of age did not differ reliably both in the control group and in the experimental one. Although, the ratio of C:T allele in juvenile girls afflicted with salpingoophoritis at the age of 15-18 years prevailed in favour of the mutant T-allele 44:72 (χ^2=6.39, p=0.041), by the non-reliable disproportion in patients at the age of 12-14 years – 22:38 (χ^2=4.95, p=0.085). TT-genotype in girls of 12-14 years was found 2.33 times more frequently than CC-genotype (χ^2=4.80, p=0.028); analogical picture is found in the teenagers of 15-18 years of age: TT-genotype was registered 2.16 times more often than CC-variant (χ^2=7.67, p=0.006), respectively (Table 2).

Table 2: Distribution of C-511T genotype polymorphism of IL-1β gene in puberty age girls with salpingoophoritis

Groups of examination		**№**	**Genotypes of IL-1β gene, n (%)**			**χ^2 p**
			CC, n=18	**TC, n=30**	**TT, n=40**	
Age of the examined patients, n (%)	12-14 years, n=30 (%)	1	6 (20.0)	10 (33.3)	14 (46.7)	χ^2=4.95 p=0.085
	15-18 years, n=58 (%)	2	12 (20.7)	20 (34.5)	26 (44.8)	χ^2=6.39 p=0.041
χ^2 p (by age)			χ^2<1.0 p>0.05	χ^2<1.0 p>0.05	χ^2<1.0 p>0.05	-
Specificity of inflammation, n (%)	Specific, n=52 (%)	1	12 (23.1)	18 (34.6)	22 (42.3)	χ^2=4.38 p=0.112
	Non-specific, n=36 (%)	2	6 (16.7)	12 (33.3)	18 (50.0)	χ^2=9.0 p=0.011
χ^2 p (by specificity of inflammation)			χ^2<1.0 p>0.05	χ^2<1.0 p>0.05	χ^2<1.0 p>0.05	-
General examined group, n=88 (%)			18 (20.5)	30 (34.1)	40 (45.4)	χ^2<1.0 p>0.05
Control group, n=31 (%)	12-14 years, n=10	1	4 (40.0)	3 (30.0)	3 (30.0)	χ^2=6.43 p=0.04
	15-18 years, n=21	2	9 (42.9)	9 (42.9)	3 (14.3)	χ^2=5.74 p=0.05
χ^2 p (control by age)			χ^2<1.0 p>0.05	χ^2<1.0 p>0.05	χ^2<1.0 p>0.05	-
General control group, n=31 (%)			13 (41.9)	12 (38.7)	6 (19.5)	χ^2=10.1 p=0.006
Total, n=119 (%)			31 (26.1)	42 (35.3)	46 (38.6)	χ^2=1.55 p>0.05

Patients with non-specific salpingoophoritis showed a reliable domination of T-allele over CC-genotype in 4.99 times (χ^2=9.0, p=0.011) (Table 2). CC-genotype in the control group of

girls at the age of 12-14 and 15-18 was registered 2 and 2,7 times more than in those of the same age with salpingoophoritis ($p<0.05$). Homozygous T-allele in healthy individuals was found in 1.56 and 3.13 times less than favourable CC-genotype. A reliable difference in the frequency of genotype distribution in the examined population was not found. Favourable CC-genotype was detected in every fifth teenager with salpingoophoritis (20.5%) and practically in every second (41.9%) from the control group. Intermediate heterozygous CT-variant was registered in every third girl (34.7%) of the examined group and among the healthy ones (38.7%). "Unfavourable" TT-genotype was present almost in half of the examined group individuals (45.4%) and only every fifth one among healthy teenagers (19.4%) (Table 2).

In afflicted teenagers the distribution of genotype frequency according to polymorphous C-511 variant of IL-1β gene corresponds to the expected Hardy-Weinberg equilibrium with unreliable tendency to heterozygous deficiency ($F=0.25$-0.28, $p>0.05$), which did not influence upon the normal population distribution in the examined population.

Distribution of 511C/T polymorphism of IL-1β gene within every age group considering specificity of inflammatory process is presented in Table 3. Reliable differences in the distribution of allele variants of the analyzed gene IL-1β in girls at the age of 12-14 years were not found. 15-18-year patients under conditions of specific inflammation did not reveal substantial changes in the distribution, although under conditions of non-specific inflammatory process mutant T-allele prevailed considerably – 32 (72.7%) over 12 (27.3%) C-allele ($\chi^2=10.4$, $p=0.006$). It should be noted that CC-genotype was more often found in teenagers with non-specific salpingoophoritis at the age of 12-14 in 2.29 times ($\chi^2=5.94$, $p=0.048$). At the age of 15-18 the situation was opposite: homozygous C-variant was found more frequently with the presence of specific inflammation in 3.06 times ($\chi^2=7.11$, $p=0.038$) (Table 3.)

Table 3: Distribution of 511C/T polymorphism of IL-1β gene in puberty age girls depending on the age and the specificity of adnexal inflammation

Patients with salpingoophoritis		**№**	**Genotypes of IL-1β gene, n (%)**			**χ^2 p**
			CC, n=18	**TC, n=30**	**TT, n=40**	
12-14 years, n=30 (%)	Specific inflammation, n=16 (%)	1	2 (12.5)	6 (37.5)	8 (50.0)	$\chi^2=5.25$ $p=0.072$
	Non-specific inflammation, n=14 (%)	2	4 (28.6)	4 (28.6)	6 (42.9)	$\chi^2<1.0$ $p>0.05$
χ^2 p			$\chi^2=5.94$ $p=0.048$	$\chi^2<1.0$ $p>0.05$	$\chi^2<1.0$ $p>0.05$	-
15-18 years, n=58 (%)	Specific inflammation, n=36 (%)	1	10 (27.8)	12 (33.3)	14 (38.9)	$\chi^2=1.0$ $p>0.05$
	Non-specific inflammation, n=22 (%)	2	2 (9.09)	8 (36.4)	12 (54.5)	$\chi^2=10.4$ $p=0.006$
χ^2 p			$\chi^2=7.11$ $p=0.038$	$\chi^2<1.0$ $p>0.05$	$\chi^2=1.35$ $p=0.24$	-

Specific salpingoophoritis is more often found in girls-carriers of CC-genotype at the age of 15-18 in 2.22 times than those at the age of 12-14 ($\chi^2=5.88$, $p=0.049$). On the contrary, non-specific

salpingoophoritis was found less in the individuals of this genotype at the age of 15-18 in 3.15 times than in teenagers with analogous genotype at the age of 12-14 (χ^2=7.22, p=0.031). Epidemiological analysis of the risk of specific or non-specific salpingoophoritis in teenage girls considering genetic content of IL-1β gene and depending on the age is presented in Table 4. Presence of C-allele is a reliable protective factor concerning the development of adnexa inflammation in girls at the age of puberty depending on its form [OR=0.31-0.43, OR 95% CI=0.16-0.81, p≤0.014-0.009], especially CC-genotype makes the chances for the development of non-specific salpingoophoritis the lowest in the examined population [OR=0.28, OR 95% CI=0.09-0.86, p=0.022]. On the contrary, T-allele increases the risk of both forms of inflammation in 1.54 and 1.72 times respectively [OR=2.34, OR 95%CI=1.23-4.45, p=0.007 i OR=3.17, OR 95%CI=1.56-6.43, p=0.002], presence of TT-genotype increases the risk of specific salpingoophoritis in 2.19 times [OR=3.06, OR 95% CI=1.07-8,71, p=0.032], and non-specific one – in 2.58 times [OR=4.17, OR 95% CI=1.38-12.6, p=0.032] respectively (Table 4).

Table 4: Genotype C-511T polymorphism of IL-1β gene, as risk factors for the appearance of a specific or non-specific salpingoophoritis in pubertal age girls

Groups		Potential Risk Factors				
		CC	TC	TT	C-allele	T-allele
Specific salpigoophoritis	RelR	0.55	0.89	2.19	0.66	1.54
	RR	0.70	0.94	1.44	0.73	1.37
	OR	0.41	0.84	3.06	0.43	2.34
	95% CI RR	0.45-1.08	0.66-1.33	1.06-1.96	0.57-0.93	1.07-1.76
	95% CI OR	0.16-1.09	0.33-2.11	1.07-8.71	0.22-0.81	1.23-4.45
	p	>0.05	>0.05	0.032	0.014	0.007
Nonspecific salpigoophoritis	RelR	0.40	0.86	2.58	0.54	1.72
	RR	0.51	0.90	1.79	0.58	1.72
	OR	0.28	0.79	4.17	0.31	3.17
	95% CI RR	0.25-1.01	0.55-1.45	1.18-2.73	0.41-0.83	1.21-2.45
	95% CI OR	0.09-0.86	0.29-2.15	1.38-12.6	0.16-0.64	1.56-6.43
	p	0.022	>0.05	0.009	0.001	0.002
Age 12-14 years	RelR	0.47	1.11	1.55	0.67	1.41
	RR	0.75	1.04	1.18	0.82	1.21
	OR	0.38	1.17	2.04	0.47	2.11
	95% CI RR	0.44-1.28	0.72-1.51	0.83-1.68	0.62-1.09	0.92-1.60
	95% CI OR	0.08-1.77	0.25-5.50	0.44-9.44	0.17-1.32	0.76-5.89
	p	>0.05	>0.05	>0.05	>0.05	>0.05
Age15-18 years	RelR	0.48	0.80	3.14	0.59	1.74
	RR	0.83	0.91	1.40	0.75	1.33
	OR	0.61	0.70	4.87	0.34	2.95
	95% CI RR	0.55-1.25	0.68-1.21	1.10-1.78	0.61-0.92	1.09-1.64
	95% CI OR	0.22-1.67	0.25-1.95	1.29-18.4	0.16-0.71	1.41-6.14
	p	>0.05	>0.05	0.013	0.003	0.006

RelR - relative risk; RR – Risk Ratio; OR – Odds Ratio; 95% CI RR, OR-(confidence interval of RR, OR.

Depending on the age it was found that T-allele and TT-genotype are the risk factors for inflammation of the adnexa in girls at the age of 15-18 [OR=2.95-4.87, OR 95% CI=1.29-18.4, p≤0.013-0.006] and they do not influence upon the development of this inflammation at the age of 12-14 regardless its form. C-allele decreases the chances to develop salpingoophoritis only at the age of 15-18 [OR=0.34, p=0.003].

Literature reports on the distribution features of genotypic variants C-511T polymorphism of IL-1β gene in populations characterized by data heterogeneity and inconsistency. Conducted racial, ethnic and population analysis showed that the incidence of homozygous mutation (TT-genotype) of IL-1β gene in our study (19.5% in control, 45.4% – in patients, 38.6% – average) corresponds to some data in Caucasians populations [8, 11, 19], in Mongoloid [20, 21] and the equatorial races [22], being higher than in Denmark Caucasians [23] and in Russian (Nanai ethnic group) [24] ($p<0.05$), indicating high populations heterogeneity after polymorphic locus of IL-1β gene. Also derived fact may be caused not only features of genotypes ethnic distribution. In the promoter area of the IL-1β gene at position 31 is another locus of frequent C/T SNP. Allelic interaction between -511 and -31 polymorphic locus can affect the genotypes options distribution.

4. Conclusion

Mutation in 511 position of the pro-motor zone of IL-1β gene (SNP id.: rs 16944) among patients with salpingoophoritis at the age of puberty is found in 45.4% cases which is in 2.33 times more often than in the individuals of the control group (p=0,01). In quantitative relation "wild" C-allele dominates in 1.63 times over the mutant T-allele in the control group (P_C=0.61 vs P_T=0.39), on the contrary, in the experimental group T-allele in 1.61 times prevails over C-alleley (P_T=0.62 проти P_C=0.38).

Among patients with non-specific salpingoophoritis the frequency of T-allele in 4.99 times prevails over CC-genotype. Specific salpingoophoritis were found in 2.22 times more frequently in girls-carriers of CC-genotype at the age of 15-18 than those at the age of 12-14. On the contrary, non-specific salpingoophoritis was found in 3.15 times less among the carriers of CC-genotype at the age of 15-18 than in those with analogical genotype at the age of 12-14.

The risk of genetically stipulated susceptibility to inflammation of the adnexa regardless of their specificity in girls at the age of puberty (especially 15-18 years) increases with presence of "mutant" T-allele and TT-genotype of IL-1β gene in 1.54-2.58 times [OR=2.34-4.17, OR 95% CI=1.07-12.6, p≤0.032-0.002], with the lowest probability of the development of inflammatory process in the adnexa among the carriers of C-allele and CC-genotype, especially non-specific salpingoophoritis [OR=0.28-0.43, p≤0.022-0.001].

5. Conflict of Interest: None declared.

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