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ASSOCIATION BETWEEN IL-1B, IL-8, IL-10 AND VEGF POLYMORPHISMS AND RISK OF ODONTOGENIC MAXILLOFACIAL INFECTIONS

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Abstract

Background. Nowadays it is being reported an increased number of cases of generalization of odontogenic infections which are caused by dental caries, periodontal diseases and other oral diseases. The beginning and progression of diseases depend on individual genetic profile of patient, but data about the role of genetic factors in purulent-inflammatory diseases of maxillofacial area pathogenesis are limited now.

The **aim** of this study was to assess the possible association between IL-1β, IL-8, IL-10 and VEGF polymorphisms and risk of odontogenic maxillofacial infections.

Materials and methods

80 patients with odontogenic maxillofacial infection (with and without diabetes mellitus) and 20 donors were examined. All patients' with odontogenic maxillofacial infection groups were operated and received antibiotic and detoxification therapy. Polymorphism in IL-1B +3954C/T (rs1143634), IL-8 -251T/A (rs4073), IL-10 -1082G/A (rs1800896) and VEGF -634 G/C (rs 2010963) were assessed by polymerase chain reaction. Odds ratio (OR) with 95% confidence interval (CI), Chi-square test were used for statistical analyses.

Results. No association observed between VEGF -634 G/C polymorphism and risk of odontogenic maxillofacial infections in patient without diabetes mellitus using all the genetic models. In patients with diabetes mellitus observed association between VEGF -634 G/C polymorphism and odontogenic maxillofacial infections in the codominant (OR=0,429, 95%CI 0,185-0,994, p=0,046), heterozygous (OR=0,167, 95%CI 0,048-0,574, p=0,004)and recessive (OR=0,194, 95%CI 0,061-0,619, p=0,005) models.

Polimorphism IL-1B +3954C/T increased the risk of odontogenic maxillofacial infections in patient without diabetes mellitus in the codominant (OR=0,059, 95%CI 0,023-0,151, p<0,001), homozygous (OR=0,021, 95%CI 0,003-0,129, p<0,001), dominant (OR=0,028, 95%CI 0,005-0,145, p<0,001) and recessive (OR=0,0074, 95%CI 0,019-0,291, p<0,001) models. Polimorphism IL-10 -1082 G/A increased the risk of odontogenic maxillofacial infections in the codominant (OR=0,356, 95%CI 0,146-0,870, p=0,021), heterozygous (OR=0,106, 95%CI 0,028-0,399, p<0,001) and recessive (OR=0,143, 95%CI 0,043-0,472, p<0,001) models. Aassociation between IL-8-251 T/A polymorphism and risk of odontogenic maxillofacial infections it was found only codominant (OR=0,444, 95%CI 0,198-1,0, p=0,048) genetic model. In these cases the risk of odontogenic maxillofacial infections were similar in patient without and with diabetes mellitus.

Conclusion. The IL-1B (+3954C/T), IL-10 (-1082G/A) polymorphism increases odontogenic maxillofacial infections risk in patient without diabetes mellitus. The IL-1B (+3954C/T), IL-10 (-1082G/A) and VEGF (-634G/C) polymorphism increases odontogenic maxillofacial infections risk in patient with diabetes mellitus.

Key words: odontogenic maxillofacial infections, IL-1B, IL-10, IL-8, VEGF, polymorphism

Introduction

Nowadays it is being reported an increased number of cases of generalization of odontogenic infections which are caused by dental caries, periodontal diseases and other oral diseases [1]. Such infections may lead to abscesses and phlegmones of maxillofacial region or, in more severe cases, to deep neck infections. The patients with acute odontogenic inflammatory diseases comprise about 50% of the whole number of patients suffering from oral diseases. When odontogenic infections are not treated properly they may lead to the patient's loss of work ability or even fatal consequences [2]. Approximately 40% of odontogenic infections result in major maxillofacial or deep neck infections [3].

The progression of odontogenic infections depends on several factors which include individual's age, underlying diseases, and immune reactivity [4]. It is believed that most of the patients suffering from odontogenic phlegmones of maxillofacial area have disorders of one or several chains of humoral or cell-mediated immunity [2].

The beginning and progression of diseases depend on individual genetic profile of patient, but data about the role of genetic factors in purulent-inflammatory diseases of maxillofacial area pathogenesis are limited now.

Given the odontogenic nature of these diseases, it is important to have a genetically determined predisposition to the aggressive course of periodontitis, which is described in more detail in the literature. The course of periodontitis can be influenced by genetically determined features of connective tissue metabolism. Thus, the processes of extracellular matrix remodeling depends on genetically determined peculiarities of matrix metalloproteinase activity, which may be determinative in beginning and course of inflammation [5]. As genes for candidates for the panel of markers of predisposition to aggressive periodontitis, genes encoding signaling factors are considered: chemokines, lymphokines [6].

In patients with different clinical course of periodontitis, features are revealed in the frequency distribution of genotypes and polymorphous variants of genes of inflammatory cytokines, in particular IL-1, IL-4, TNF-α [7, 8], nuclear transcription factor NF-KB1 [9], expression of markers of pulmonary receptors is different [10]. Changes in production of proinflammatory and anti-inflammatory cytokines can adversely affect the phagocytic tissue protection and create the preconditions for development of suppurative and inflammatory complications, which is extremely important in conditions of diabetes mellitus, in which the activity of macrophages and neutrophils is decreased [11, 12]. Thus, in patients with periodontitis with the second type of diabetes mellitus, higher non-stimulated levels of IL-6, IL-1, TNF, interferon, IL-10, IL-8, macrophage inflammatory protein 1α (MIP1α) and 1β (MIP1β) were observed, and higher stimulated levels of IL-6, IL-8, IL-10, MIP1α and MIP1β, along with lower unstimulated and stimulated levels of colony-stimulating factor granulocytes and macrophages compared with patients without diabetes. It is important to note that the induced levels of IL-6, IL-8, IL-10 and MIP1α strongly correlated with the severity of the disease [13].

The presented data indicate a possible risk of development of purulent-inflammatory diseases of maxillofacial area in patients with polymorphism of genes for pro and anti-inflammatory cytokines, which requires further research.

The **aim** of this study was to assess the possible association between IL-1β, IL-8, IL-10 and VEGF polymorphisms and risk of odontogenic maxillofacial infections.

Materials and methods. Clinical studies were performed in the State Establishment «The Institute of Stomatology and Maxillofacial Surgery of the National Academy of Medical Science of Ukraine in the informed consent of patients. 80 patients with odontogenic maxillofacial infection and 20 healthy donors were examined. Monitoring groups: 1) patients without diabetes mellitus (n=40); 2) patients with diabetes mellitus (n=40). Control group – patient without any dental disease and without diabetes mellitus. All patients of the group1 and group2 were operated and received antibiotic and detoxification therapy.

Polymorphism in IL-1B +3954C/T (rs1143634), IL-8 -251T/A (rs4073), IL-10 -1082G/A (rs1800896) and VEGF -634 G/C (rs 2010963) were assessed by polymerase chain reaction.

Odds ratio (OR) with 95% confidence interval (CI) were used to assess the strength of the association between the IL-1B +3954C/T, IL-8 251T/A, IL-10 -1082G/A and VEGF -634 G/C polymorphisms and the risk of odontogenic maxillofacial infections in codominant, heterozygous, homozygous, recessive and dominant genetic models based on genotype frequencies in cases and controls. All P values were 2-sided, $p<0,05$ was considered to be statistically significant. All statistical analyses were conducted using free statistical package on www.medstatistic.ru.

Results. As a result of the studies, the frequency of different genotypes of the genes VEGF-634 G / C, IL-1B + 3954C / T, IL-10 -1082G / A was revealed in patients with purulent-inflammatory diseases of the maxillofacial region and patients of the control group (tabl. 1). There were no differences in frequency of different genotypes of IL-8 251T / A. There was a decreasing in the frequency of the genotype of the CC gene of the VEGF gene in patients with odontogenic maxillofacial infections and with diabetes mellitus in comparison with the patient without diabetes mellitus.

No association observed between VEGF -634 G/C polymorphism and risk of odontogenic maxillofacial infections in patient without diabetes mellitus using all the genetic models (tabl. 2). In patients with diabetes mellitus observed association between VEGF -634 G/C polymorphism and odontogenic maxillofacial infections in the codominant, heterozygous and recessive models (tabl. 3).

Tabl. 1. The genotype frequency in patient with odontogenic maxillofacial infections without diabetes mellitus (cases 1) and with diabetes mellitus (cases 2).

Polymorphism		Cases 1 (n=40)	%	Cases 2 (n=40)	%	Controls (n=20)	%
VEGF -634 G/C	CC	18	45	9*#	22,5	12	60
	CG	21	52,5	27*	67,5	6	30
	GG	1	2,5	4	10	2	10
IL-1B +3954C/T	CC	4*	10	3*	7,5	12	60
	CT	4	10	6	15	6	30
	TT	32*	80	31*	77,5	2	10
IL-8 251T/A	TT	7	17,5	6	15	6	30
	TA	18	45	20	50	9	45
	AA	15	37,5	14	35	5	25
IL-10 -1082G/A	GG	10*	25	8*	20	14	35
	GA	27*	67,5	28*	70	4	20
	AA	3	7,5	4	10	2	10

- * - $p<0,05$ in comparing with control group
- # - $p<0,05$ in comparing between group 1 and group 2.

Polimorphism IL-1B +3954C/T increased the risk of odontogenic maxillofacial infections in the codominant, homozygous, dominant and recessive models. Polimorphism IL-10 -1082 G/A increased the risk of odontogenic maxillofacial infections in the codominant, heterozygous and recessive models. Aassociation between IL-8-251 T/A polymorphism and risk of odontogenic maxillofacial infections it was found only codominant genetic model.

Discussion. VEGF is considered to be the major factor inducing the growth of blood vessels, which is essential during wound healing and tissue remodeling [14]. VEGF signaling regulates organ homeostasis in adults [15]. Allele C is associated with increased production of VEGF. In our studies, it was established that allele G is associated with lower VEGF production in patients with odontogenic maxillofacial infections and diabetes mellitus. Due to odontogenic nature of maxillofacial infection, a possibly low level of VEGF promotes the spread of infection from damaged periodontal tissues. It is possible that a low level of VEGF can affect the regeneration of tissues during the course of an acute inflammatory process, change the clinical picture of odontogenic maxillofacial infections, but this requires additional research.

Interleukins (IL) is the large family of signaling molecules (cytokines) which provide ‘communication’ between the various cells participating in the immune reactions. The mutations of genes encoding particular types of interleukins are linked with the fast progression and predisposition to complications of inflammatory processes [16]. The current

research is focused on studying of the role of mutations of the genes encoding IL1-B, IL-8, IL-10 in progression of the odontogenic infections of the maxillofacial region.

IL1-B is produced by activated macrophages and controls cell differentiation, proliferation and apoptosis and is believed to contribute to inflammatory hypersensitivity [17]. Dereca X. at. all., 2102, established that IL-1A (-899), IL-1B (+3954) gene polymorphism were increased periimplant tissue infection and destruction [18]. Hamdy A.A. and Ebrahem, 2011 studied possible association of IL-1A (-899), IL-1B (+3954) genotypes with peri-implantitis progression. They established association between polymorphism IL-1A (-899), IL-1B (+3954) and greater tissue destruction in patients with inflamed periodontal or peri-implant tissue acts [19]. In our studies, it was established that the T allele of the IL-1 gene ($p < 0.001$) is more common, which is accompanied by an increased production of this interleukin in patients with odontogenic maxillofacial infection. It can be assumed that large degree of tissue damage in inflammatory periodontal diseases promotes the spread of infection and occurrence of odontogenic maxillofacial infection.

Chen at all., 2018, determined associations between polymorphism IL-1B (+3954) and recurrent aphthous stomatitis risk, IL-10-1082 G/A polymorphism has protective effect [20]. In our investigation were studied that polymorphism IL-10 in codominant ($p=0,021$), heterozygous ($p< 0,001$) and recessive ($p< 0,001$) models increased the risk of odontogenic maxillofacial infections. This data requires further study of mechanisms of higher risk of odontogenic maxillofacial infection in patients with polymorphism of IL-1 and IL-10.

Aassociation between IL-8-251 T/A polymorphism and risk of odontogenic maxillofacial infections it was found only codominant genetic model (OR=0,444; 95% CI 0,198-1,0; $p=0,048$) and requires further study.

Conclusion. The IL-1B (+3954C/T), IL-10 (-1082G/A) polymorphism increases odontogenic maxillofacial infections risk in patient without diabetes mellitus. The IL-1B (+3954C/T), IL-10 (-1082G/A) and VEGF (-634G/C) polymorphism increases odontogenic maxillofacial infections risk in patient with diabetes mellitus.

Tabl. 2. Association between VEGF, IL-1B, IL-8 and IL-10 polymorphisms and risk of odontogenic maxillofacial infections in patient without diabetes mellitus

Polymorphism	Dominant model			Recessive model			Homozygous model			Heterozygous model			Codominant model		
	OR (95% CI)	χ^2	P values	OR (95% CI)	χ^2	P values	OR (95% CI)	χ^2	P values	OR (95% CI)	χ^2	P values	OR (95% CI)	χ^2	P values
VEGF -634 G/C (rs2010963)	(GC + CC) vs. GG			CC vs. (GC + GG)			CC vs. GG			GC vs. CC			C vs. G		
	4,333 (0.369-50,955)	1,579	0,209	0,545 (0.183-1.623)	1,2	0,274	3,0(0.244-36,884)	0,794	0,373	0,429 (0,134-1,974)	2,079	0,15	0,826 (0.348-1.960)	0,188	0,665
IL-1B +3954C/T (rs1143634)	(CC + CT) vs. TT			CC vs. (CT + TT)			CC vs. TT			CC vs. CT			C vs. T		
	0,028 (0,005-0,145)	26,606	<0,001	0,074 (0,019-0,291)	17,045	<0,001	0,021 (0,003-0,129)	25,782	<0,001	0,5 (0,092-2,73)	0,65	0,421	0,059 (0,023-0,151)	42,198	<0,001
IL-8 251T/A (rs4073)	(TT + TA) vs. AA			TT vs. (TA + AA)			TT vs. AA			TT vs. TA			T vs. A		
	0,556 (0,168-1,840)	0,937	0,333	0,495 (0,141-1,740)	1,227	0,268	0,389 (0,088-1,722)	1,587	0,208	0,583 (0,151-2,256)	0,615	0,433	0,444 (0,198-1,0)	3,92	0,048
IL-10 -1082G/A (rs1800896)	(GG + GA) vs. AA			GG vs. (GA + AA)			GG vs. AA			GG vs. GA			G vs. A		
	1,37 (0,210-8,943)	0,109	0,742	0,143 (0,043-0,472)	11,25	<0,001	0,476 (0,067-3,396)	0,562	0,454	0,106 (0,028-0,399)	12,681	<0,001	0,356 (0,146-0,87)	5,354	0,021

Tabl. 3. Association between VEGF, IL-1B, IL-8 and IL-10 polymorphisms and risk of odontogenic maxillofacial infections in patient with diabetes mellitus

Polymorphism	Dominant model			Recessive model			Homozygous model			Heterozygous model			Codominant model		
	OR (95% CI)	χ^2	P values	OR (95% CI)	χ^2	P values	OR (95% CI)	χ^2	P values	OR (95% CI)	χ^2	P values	OR (95% CI)	χ^2	P values
VEGF -634 G/C (rs2010963)	(GC + CC) vs. GG			CC vs. (GC + GG)			CC vs. GG			GC vs. CC			C vs. G		
	1,0 (0,167-5,985)	0,0001	1,0	0,194 (0,061-0,619)	8,242	0,005	0,375 (0.056-2,519)	1,06	0,572	0,167 (0,048-0,574)	8,776	0004	0,429 (0.185-0,994)	4,0	0,046
IL-1B +3954C/T (rs1143634)	(CC + CT) vs. TT			CC vs. (CT + TT)			CC vs. TT			CC vs. CT			C vs. T		
	0,032 (0,006-0,166)	24,545	<0,001	0,054 (0,012-0,237)	19,6	<0,001	0,016 (0,002-0,109)	48,54	<0,001	0,25 (0,046-1,365)	2,7	0,101	0,059 (0,023-0,151)	42,198	<0,001
IL-8 251T/A (rs4073)	(TT + TA) vs. AA			TT vs. (TA + AA)			TT vs. AA			TT vs. TA			T vs. A		
	0,619 (0,186-2,061)	0,616	0,433	0,412 (0,113-1,498)	1,875	0,171	0,357 (0,078-1,640)	1,802	0,18	0,450 (0,113-1,786)	1,316	0,252	0,444 (0,198-1,0)	3,92	0,048
IL-10 -1082G/A (rs1800896)	(GG + GA) vs. AA			GG vs. (GA + AA)			GG vs. AA			GG vs. GA			G vs. A		
	1,0 (0,167-5,985)	0,0001	1,0	0,107 (0,031-0,367)	16,632	<0,001	0,286 (0,042-1,923)	1,768	0,184	0,082 (0,021-0,318)	15,341	<0,001	0,306 (0,125-0,745)	7,177	0,008

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