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The Role of Hereditary Load in the Nature of Associations of Genetic Polymorphism *-308G/A TNFα, +250A/G Ltα, +36A/G TNFR1* and *+1663A/G TNFR2* with Formation of Chronic True Eczema.

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ABSTRACT

The article presents data about the influence of hereditary load on the nature of associations of candidate genes with formation of chronic true eczema (CTE). There were established associations of genetic polymorphism *+1663A/G TNFR2* in individuals with hereditary load and of *-308G/A TNFα, +250A/G Ltα* in individuals without burdened familial history with formation of chronic true eczema among the natives of the Central Black Earth Region of the Russian Federation.

Keywords: chronic true eczema, tumor necrosis factors, genetic variations, polymorphism.

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INTRODUCTION

True eczema is an allergic inflammatory dermal disease usually having chronic nature and aggravations, it is induced by various exogenous and endogenous factors and characterized by polymorphism of the elements among which vesicles take the first place. Eczema takes 30-40% of all of the dermatopathies. According to statements of different authors the disease incidence varies from 6.0 to 15.0 cases per 1000 people [1].

According to the up-to-date concepts the main role in eczema progression is being played by T-lymphocytes having specific surface receptors for antigen and secreting a range of anti-inflammatory cytokines: IL-1, IL-2, *TNFα* [2]. Release of bioactive substances results in development of inflammatory tissue reaction which is clinically manifested by an allergy response in the form of hyperemia, edema, itching. Antigen stimulation of Th1 results in synthesis of IL-2, moreover the IL-2 producing capacity of CD4-cells in sick people is higher then in health ones [3].

Inflammatory cytokines activate induction of adhesion molecules expression on leukocytes and endothelial cells in consequence of which an inflow of leukocytes from a vascular bed to an inflammation focus by way of their transendothelial migration is being stimulated [4]. The following transportation and accumulation of immune competent cells in an inflammation focus is being controlled by chemokines which are produced by macrophages and endothelial cells [5]. Infiltrating cells in a focus of inflammation consisting of neutrophils, eosinophils and macrophages promote further progression of allergic inflammation [6]. Polymorphous infiltration in the skin in case of eczema is a result of action of the generated anti-inflammatory cytokines, inclusive of *TNFα* [7].

MATERIALS AND METHODS

An experimental panel included 552 persons: 230 patients with chronic true eczema and 322 persons of a control panel. As of the moment of examination the burdened familial history was detected in 80 patients (34.78%) among the total number of 230 patients, the rest 150 patients (65.22%) with CTE didn't have hereditary load. The examined panels included individuals of Russian nationality who were the natives of the Central Black Earth Region of the Russian Federation and had no blood relationship with each other.

Criteria of inclusion into the investigated sampling populations: individuals of Russian nationality who were natives of the Central Black Earth Region of the Russian Federation and had no blood relationship with each other; voluntary consent of the patients for experiment; the patients were enrolled to the experimental panel only after their diagnosis was determined. The diagnosis was established on the basis of complaints, past medical history, clinical aspects, state of disease and laboratory-based test methods [8]. The control panel included persons without dermatopathies at the moment of examination as well as without somatic pathology resulting in secondary skin lesions.

Criteria of exclusion from the investigated sampling populations: patients with other form of eczema; patients with chronic true eczema accompanied by other dermatopathy or somatic disease affecting the state of skin; presence of severe somatopathy (oncological diseases, rheumatoid disease, Crohn's disease), as well as patients regularly taking antihistamines, steroids, immunosuppressive drugs; patients under age of 18; individuals who refused to participate in the investigation.

All of the patients with CTE and the individuals from the control panel were subject to typing of genetic polymorphisms of tumor necrosis factor α (*-308G/A TNFα*), лимфотоксин *α* (*+250A/G Ltα*), tumor necrosis factor receptors of the 1st and the 2nd type *(+36 A/G TNFR1* and *+1663A/G TNFR2)*.

Venous blood in the amount of 8-9 ml taken from the proband cubital vein served as material for the investigation. Venous blood samples were taken into test tubes with a preservative containing 0.5M EDTA solution (pH=8.0). Separation of genomic DNA from peripheral blood was carried out by the method of phenol-chloroform extraction [9].

Analysis of the candidate gene loci was performed by polymerase chain reaction (PCR) of DNA synthesis. PCR was carried out by means of IQ 5 (Bio-Rad) amplifier in a real time mode with use of DNA-

polymerase Thermus aquaticus made by "Sileks-M" company and oligonucleotide primers and probes synthesized by "Syntol" company. Genotyping of DNA marker was made by the method of allelic discrimination assay with use of Taq Man probes.

χ^2 criterion was used for analysis of correspondence between the observed and the expected genotype distributions based on Hardy-Weinberg equilibrium model. Associations of alleles and genotypes of the examined DNA markers with formation of chronic true eczema were evaluated by means of 2x2 contingency tables analysis accompanied by calculation of χ^2 criterion with Yates correction for continuity and odds ratio (OR) with 95% confidence intervals (CI) [10].

RESULTS

The study of genotype distribution of the examined polymorphous markers demonstrated that for all considered markers in the control sampling population and in the panel with the patients having chronic true eczema empirical genotype distribution corresponded to theoretically expected one subject to Hardy-Weinberg equilibrium (p>0.05) (Table 1).

Table 1: Summary information about the studied polymorphisms.

Polymorphism	Studied groups	Minor allele	MAF (%)	HWE	
				$ч^2$	p
(-308) G/A TNFб	Case	*(-308) A TNFб*	14.35	1,68	>0.05
(-308) G/A TNFб	Control	*(-308) A TNFб*	10.47	0,09	>0.05
(+250) A/G Ltα	Case	*(+250) G Ltα*	30.05	0.53	>0.05
(+250) A/G Ltα	Control	*(+250) G Ltα*	24.38	3.44	>0.05
(+36) A/G TNFR1	Case	*(+36) A TNFR1*	47.82	0.65	>0.05
(+36) A/G TNFR1	Control	*(+36) A TNFR1*	49.53	0.38	>0.05
***(+**1663) A/G TNFR2*	Case	***(+**1663) A TNFR2*	39.27	0.03	>0.05
***(+**1663) A/G TNFR2*	Control	***(+**1663) A TNFR2*	44,05	3.10	>0.05

Notes: MAF, minor allele frequency; Hardy-Weinberg equilibrium. P values were calculated using the χ^2 test.

In the group of patients having CTE but not having burdened familial history genetic polymorphisms -*308G/A TNFα* and *+250A/G Ltα* contribute significantly to susceptibility to CTE. In this group of patients the concentrations of genetic variations *308A TNFα* (15.44%), *+250G Ltα* (32.73%), *+250GG Ltα* (10.80%) are positively higher then in the control panel where the mentioned indices made 10.47% (χ^2=4.03, p=0.04, OR=1.56, 95% CI 1.01-2.41), 24,38% (χ^2=6.48, p=0.01, OR=1.51, 95% CI 1.1-2.08) and 4.04% (χ^2=6.63, p=0.01, p_{cor}=0.03, OR=2.88, 95% CI 1.25-6,64) correspondingly.

Among the patients with CTE having hereditary load susceptibility to CTE is connected with genetic polymorphism *+1663A/G TNFR2*: genetic variation frequency *+1663G TNFR2* in the patients panel (66.67%) is by 1.2 times higher then the similar index in the control panel (55.95%, χ^2=5.08, p=0.025, OR=1.58, 95% CI 1.06-2.35).

FINDINGS

We have established peculiarities of susceptibility to formation of CTE in individuals depending on burdened familial history: susceptibility of individuals with burdened familial history to CTE progression is connected with genetic polymorphism *+1663A/G TNFR2,* whereas susceptibility of individuals without hereditary load to CTE formation is determined by polymorph markers *-308G / A TNFα* and *+250 A/G Ltα.*

The received data on involvement of genetic polymorphisms of tumor necrosis factor in CTE formation are in agreement with literature materials on the functional significance of these cytokines in the body. In accordance with data from the literature lymphotoxin α and tumor necrosis factor α participate in

realization of a wide range of biomedical effects in the body (cytotoxic action, influence on immune reaction development, promote immune inflammatory responses, promote formation of peroxide-ions in neutrophils, act as chemoattractants for them, promote activity of fibroblasts etc.). These biomedical effects have great importance for etiopathogenesis of chronic true eczema which is associated with active proliferation of pathological clone of lymphocytes, immune system disbalance formation and bacterial complications progression.

CONCLUSION

Therefore it was ascertained that genetic variations *-308A TNF*α (OR=1.56), *+250G Ltα* (OR=1.51) and *+250GG Ltα* (OR=2.88) are CTE formation risk factors for individuals without burdened familial history. For individuals with hereditary load *+1663G TNFR2* (OR=1.58) serves as a CTE formation risk factor.

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