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Prognostic Value of Polymorphism of G-308A Gene of the Tumor Necrosis Factor-α in the Progression of Chronic Heart Failure in Patients with Ischemic Heart Disease and Obesity

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Abstract.

One of the widespread and prognostically unfavorable complications of cardiovascular diseases is chronic heart failure, where an important role is given to proinflammatory cytokines in the pathogenesis of the disease. Polymorphic variants of the gene of tumor necrosis factor-α are determinants of increased risk in the development of chronic heart failure in patients with ischemic heart disease. Presence of allelic gene A and genotype A/A of polymorphic locus G-308A, the gene of tumor necrosis factor-α in patients with ischemic heart disease and concomitant obesity was associated with chronic heart failure progressing and development of systolic dysfunction of the left ventricle.

Problem statement and analysis of the recent research

Chronic heart failure (CHF) is one of the common and prognostically adverse complications of cardiovascular system diseases [8].

A lot of researches are devoted to relation of genes polymorphisms with the most common cardiovascular diseases (CVD) and activity of prescribed treatment for this patient group. Analysis of national and foreign literature shows that outstanding interest is attracted by the study of polymorphisms of genes encoding proteins which are a part of the structure of enzymes, hormones and neurohormonal systems receptors and are involved in the development and progression of most cardiovascular diseases, including CHF[1, 5 6].

Regarding CHF pathogenesis, the role of proinflammatory cytokines should not go unmentioned.

The literature provides relatively few data on the association of genes polymorphisms encoding proinflammatory cytokines with CVD development. Researches on the relation of these polymorphisms with the risk of CHF and character of its progression in patients with coronary artery disease are rare.

Thus, S. N. Shilov et al. showed in their work that polymorphic variants of the gene of tumor necrosis factor-α (TNF-α) (G-308A) are not only determinants of increased risk of CHF in patients with coronary artery disease (CAD), but also are associated with the severity and nature of CHF course in these patients [4]. No associations between plasma concentrations of TNF-α and gene polymorphism of TNF-α (308 A / G, 238 A / G) were observed in another study, which included more than 266 patients with CHF and ejection fraction (EF) below 40% [11].

Contradictory data obtained are probably due to the lack of large randomized studies on this issue. This again emphasizes the need for further study of genes polymorphisms encoding proinflammatory cytokines and their influence on the formation and progression of cardiovascular diseases and CHF.

The objective of the research was to evaluate the role of polymorphism of G-308A gene of tumor necrosis factor - α as a possible factor in the progression of chronic heart failure in patients with coronary artery disease and obesity.

Materials and methods of the research

The study included a comprehensive examination of 222 patients with coronary artery disease and obesity who were treated in the cardiology department of Kharkiv City Hospital №27, which is the teaching health care facility of Department of Internal Medicine and Clinical Immunology and Allergology №2 of Kharkiv National Medical University of Ministry of Health of Ukraine. Comparison group consisted of 115 patients with coronary artery disease with normal body weight. The control group included 35 apparently healthy individuals. The groups were compared by age and sex. The study excluded patients with severe concomitant diseases of the respiratory and digestive systems, kidneys and those with cancer.

The diagnosis was made in accordance with valid orders of Ministry of Health of Ukraine.

All patients underwent general clinical and instrumental examination.

Research of the polymorphic locus of G-308A TNF-α gene was performed by the method of polymerase chain reaction with results electrophoretic detection using reagent kits “SNP-Express” manufactured by Ltd. “Liteh” (Russia). DNA isolation from blood was performed using the reagent "DNA EXPRESS" produced by SPC "Liteh" (Russia) according to the instructions. The correctness of the frequency distribution of genotypes was determined by the correspondence of Hardy-Weinberg equilibrium (pi2 + 2 pipj + pj2 = 1). According to the Helsinki Declaration, all patients were informed about the clinical trial and agreed to determine investigated gene polymorphisms.

Statistical data processing was conducted using the package Statistica, version 6.0. χ2 Pearson and Fisher criteria was used to compare the distribution of genotypes and allele frequencies between groups. The odds ratio (OR) was calculated to determine the relative risk of diseases. OR = 1 was considered as no association; OR>1 considered as a positive association; OR <1 was considered as negative allele or genotype association with disease (low risk of the disease). Credible interval (CI) is an interval of values within which OR prognostic value of is found with a probability of 95%. Statistically significant differences were considered at p<0.05.

Results of the research and their discussion

The impact of polymorphic locus G-308A TNF-α gene on the CHF progression in patients with coronary artery disease and obesity was studied. The results are presented in Table 1.

In patients with coronary artery disease and obesity CHF progression from FC I to FC II was characterized by increased frequency of polymorphic locus A allele G-308A TNF-α gene by 10.92% and A/A genotype by 11.05% (34% versus 44. 92% and 22% versus 33.05%) and a decrease in the frequency of G allele by 10.92% and G/G genotype by 10.33% (55.08% vs 66% and 40% vs. 29.67%). CHF progression from FC II to FC III-IV was characterized by a decrease by 10.37% detection rate of G/G genotype (40% vs. 29.63%) (p<0.05). CHF progression from FC I to FC III-IV was characterized by improbable increase in frequency of A allele and A/A genotype (34% versus 40.74% and 27.78% against 22%) and from FC II to FC III-IV by improbable decrease in frequency of A allele and A/A genotype (44.92% versus 40.74% and 33.05% against 27.78%) (p>0.05). Increase in FC of CHF showed no connection with G/A genotype.

Table 1

The frequency of alleles and genotypes of polymorphic loci G-308A of TNF-α gene according to FC of CHF in patients with coronary artery disease and obesity

Genetic markers	Subgroup 1 FC I of CHF (N = 50)	Subgroup 2 FC II of CHF (N = 118)	Subgroup 3 FC III-IV of CHF **(N = 54)**
A Allele	**17 (34 %)**	**53 (44.92 %)***	**22 (40.74 %)**
G Allele	**33 (66 %)**	**65 (55.08 %)***	**32 (59.25 %)**
G/A Genotype	**19 (38 %)**	**44 (37.28 %)**	**23 (42.59 %)**
A/A Genotype	**11 (22 %)**	**39 (33.05 %)***	**15 (27.78 %)**
G/G Genotype	**20 (40 %)**	**35 (29.67 %)***	**16 (29.63 %)***

Note. *- the probability of differences with subgroup 1 (p<0.05).

Indicated dynamics can be explained by the fact that A allele carriership, as it has been proven, is associated with higher levels of TNF-α, compared with homozygotes for G allele [16]. The reasons for increase in the level of circulating cytokines in case of CHF are not completely studied, but increased expression of cytokines in the myocardium was found at the later stages of the disease [2, 3, 7]. Myocardial contribution of immunopeptides products to increase in cytokines level in serum is limited due to poor diffusion of cytokines in coronary blood flow. The increase in CHF cytokine aggression is supposed to be caused by systemic tissue hypoxia determining systemic inflammation development [10]. This cytokines dynamic suggests exhaustion of retention mechanisms of cachexia.

The distribution of frequencies of alleles and genotypes of polymorphic loci G-308A TNF-α gene depending on LVEF in patients with CHF that occurred on the background of CHD with concomitant obesity are presented in Table 2.

A allele carriership (56 (46.28%) versus 34 (33.66%)) was observed significantly more often by 12.62% in patients with coronary artery disease and obesity with EF<45% and allele G carriership (65 (53.72 %) versus 66 (66.34%)) was observed less often compared with patients whose ejection fraction was higher than 45% (p<0.05). A allele in patients with LV systolic dysfunction was almost equally detected in homozygous and heterozygous forms - 44 (36.37%) and 47 (38.84%), respectively. However, heterozygous genotype dominated (32 (32.68%)) in patients with preserved ability myocardial contraction compared to homozygous (22 (21.78%)). Comparing the distribution of genotypes in subgroups it should be noted that A/A genotype was detected in patients with coronary artery disease and obesity with systolic dysfunction by 14.59% more often than in patients with EF> 45% (44 (36.37%) versus 22 (21.78%)), and G/G genotype was observed less often by 20.75% (30 (24.79%) versus 46 (45.54%)) (p<0.05).

Table 2

The frequency of alleles and genotypes of polymorphic loci G-308A TNF-α gene depending on LVEF in patients with coronary artery disease and obesity

Genetic markers	Subgroup 1 EF>45% (N = 101)	Subgroup 2 EF<45% (N = 121)
A Allele	**34 (33.66 %)**	**56 (46.28 %)***
G Allele	**66 (66.34 %)**	**65 (53.72 %)***
G/A Genotype	**32 (32.68 %)**	**47 (38.84 %)**
A/A Genotype	**22 (21.78 %)**	**44 (36.37 %)***
G/G Genotype	**46 (45.54 %)**	**30 (24.79 %)***

Note. *- the probabilit of differences between subgroups (p<0.05).

Thus, the formation of systolic dysfunction in patients with CHF on the background of CHD in case of combined course and obesity is associated with A allele and A/A genotype of TNF-α gene (G-308A).

According to the literature, -308A allele is associated with a 6-7-fold increase in the level of gene transcription of TNF-α compared to the -308G allele, which has a protective value for the clinical course of the disease [13, 14, 17]. As a result, more clear manifestation of their biomedical effects (pro-inflammatory and cytotoxic effects, endothelial dysfunction, activating hemostasis system, induce apoptosis, etc.) may be expected in patients with high-performance -308A allele of TNF-α gene [9, 12, 15].

Conclusions

A allele and A/A genotype of polymorphic locus G-308A TNF-α gene in patients with coronary artery disease with concomitant obesity was associated with progression of CHF, the formation of LV systolic dysfunction.

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