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DEVELOPMENT AND PROGRESSION OF OBESITY IN PATIENTS WITH CORONARY HEART DISEASE: EMPHASIS ON LEPTIN GENE POLYMORPHISM (Arg223Gln)

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The article assesses the contribution of leptin gene polymorphism (Arg223Gln) in the development and progression of obesity in patients with coronary heart disease. 222 patients with coronary heart disease and obesity were surveyed. The study of leptin gene polymorphic locus Arg223Gln was performed by polymerase chain reaction of all examined patients. G allele and G/G genotype of the leptin gene polymorphism (Arg223Gln) are more common among the patients with coronary heart disease and obesity and the frequency of their detection increases with the growth of the degree of obesity.

KEY WORDS: leptin gene polymorphism, obesity, coronary heart disease

РОЗВИТОК ТА ПРОГРЕСУВАННЯ ОЖИРІННЯ У ХВОРИХ НА ІШЕМІЧНУ ХВОРОБУ СЕРЦЯ: АКЦЕНТ НА ПОЛІМОРФІЗМ ГЕНА ЛЕПТИНУ (Arg223Gln)

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У статті оцінено внесок поліморфізму гена лептину (Arg223Gln) у розвиток і прогресування ожиріння у хворих на ішемічну хворобу серця. Обстежено 222 хворих на ішемічну хворобу серця й ожиріння. Дослідження поліморфного локусу Arg223Gln гена лептину проводили методом полімеразної ланцюгової реакції всім обстеженим хворим. Серед хворих на ішемічну хворобу серця й ожиріння частіше зустрічаються алель G і G/G генотип поліморфізму гена лептину (Arg223Gln), причому частота їх виявлення збільшується відповідно зростанню ступеня ожиріння.

КЛЮЧОВІ СЛОВА: поліморфізм гена лептину, ожиріння, ішемічна хвороба серця

РАЗВИТИЕ И ПРОГРЕССИРОВАНИЕ ОЖИРЕНИЯ У БОЛЬНЫХ ИШЕМИЧЕСКОЙ БОЛЕЗНЬЮ СЕРДЦА: АКЦЕНТ НА ПОЛИМОРФИЗМ ГЕНА ЛЕПТИНА (Arg223Gln)

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В статье оценено вклад полиморфизма гена лептина (Arg223Gln) в развитие и прогрессирование ожирения у больных ишемической болезнью сердца. Обследовано 222 больных ишемической болезнью сердца и ожирением. Определение полиморфного локуса Arg223Gln гена лептина проводили методом полимеразной цепной реакции всем обследованным больным. Среди больных ишемической болезнью сердца и ожирением чаще встречался аллель G и G/G генотип полиморфизма гена лептина (Arg223Gln), причем частота их выявления увеличивалась соответственно увеличению степени ожирения.

КЛЮЧЕВЫЕ СЛОВА: полиморфизм гена лептина, ожирение, ишемическая болезнь сердца

INTRODUCTION

Obesity is one of the most pressing health and social problems, which is characterized by the world health organization as a non-infectious epidemic. Up to present, the obesity pathogenesis causes debate among scientists. However, after the discovery of leptin the number of studies dealing with the problem increases. In addition, leptin significantly

influences on the atherosclerotic process, the harbingers of which is obesity [1].

Today, the interest of scientists is confined to the definition of the pathogenetic role of gene polymorphisms, especially in the context of combined course of coronary heart disease (CHD) and obesity.

The results of studies examining the influence of leptin gene polymorphism on the development of obesity are controversial [2–3], and Ukrainian populations are not defined.

OBJECTIVE

The aim of the study is to evaluate the contribution of leptin gene polymorphism (Arg223Gln) in the development and progression of obesity in patients with coronary heart disease in the Ukrainian population.

MATERIALS AND METHODS

With the purpose to study the problem the comprehensive examination of 222 patients with coronary artery disease and obesity was carried. The patients included were treated in the Cardiology Department of the Kharkiv Clinical hospital № 27, which is the basic medical institution of Internal Medicine № 2 and Clinical Immunology and Allergology of Kharkiv National Medical University of Ministry of Health of Ukraine. The comparison group consisted of 115 CHD patients with normal body weight. The control group consisted of 35 practically healthy people. Additionally, patients of IHD and obesity were divided into subgroups depending on the degree of the last: the first subgroup consisted of 80 patients with obesity of the 1-st degree, the second group consisted of 71 patients with obesity of the 2-nd degree, the third – 71 patients with obesity of the 3-d degree. Groups were matched in accordance age and sex. The study excluded patients with severe concomitant pathology of the respiratory system, digestive system, kidneys and individuals with cancer.

The diagnosis was established in accordance with the applicable orders of the Ministry of Health of Ukraine.

All patients were undergone general clinical and instrumental examination. For the characteristics of obesity body mass index (BMI) (Quetelet index), which was calculated with the formula: weight (kg)/height (m2), was determined.

The study of leptin gene polymorphic locus Arg223Gln was performed by polymerase chain reaction with electrophoresis detection of the results using sets of reagents «SNP-EXPRESS» produced by NPF «Ltah» (RF). Extraction of DNA from whole blood was performed using a reagent «DNA-Express-blood» produced by NPF «Ltah» (Russian Federation) according to the instructions. The correctness of the distribution of genotypes was determined under Hardy-Weinberg equilibrium (pi2 + 2 pipj + pj2 = 1). In accordance with the Helsinki Declaration, all patients were informed about the clinical trial and gave consent for determination of polymorphism of the studied gene.

Statistical data processing was performed using Statistica package, version 6.0. For comparison of the frequency distribution of alleles and genotypes between groups $\chi 2$ Pearson and Fisher criteria were used. To determine the relative risk odds ratio (OR) was calculated. As the lack of association VSH=1 was considered; as a positive association – VSH > 1; negative association of allele or genotype with the disease (low disease risk) VSH < 1 was considered. Confidence interval (CI) is an interval of values within which with 95 % probability the predictive value of VSH presents. Statistically significant differences were considered at $p < 0.05$ were considered.

RESULTS AND DISCUSSION

The development of obesity in patients with coronary artery disease in the Ukrainian population was connected due to the results of our study with G allele and G/G genotype leptin gene polymorphism (Arg223Gln) (Table. 1).

The presence of G allele and G/G genotype of the leptin gene polymorphism (Arg223Gln) in CHD patients was associated with the development of obesity, respectively (OR = 1,70, 95 % CI = [1,26–2,31], $\chi 2$=11.8, $p < 0.05$) and (OR = 2,77; 95 % CI = [1,50–5,12], $\chi 2$=10,9; $p < 0.05$).

Table 1

The value of G allele and G/G genotype of leptin gene polymorphism (Arg223Gln) in the development of obesity in CHD patients

Genetic markers	OSH (95 % CI)
The G Allele of	1,70 (1,26–2,31)
	$\chi^2 = 11,8$; $p < 0,05$
Genotype of G/G	2,77 (1,50–5,12)
	$\chi^2 = 10,9$; $p < 0,05$

We carried out the determination of the frequency of alleles and genotypes of leptin gene polymorphism (Arg223Gln) depending on BMI in patients with CHD and obesity based on the previous data (tab. 2).

32 patients with coronary artery disease and obesity of the 1-st degree were carriers of A allele, that was equal to 40 %, G allele – 48 patients (60 %). A/A genotypes, G/A and G/G genotypes had 18 (22,5 %), 30 (37,5 %) and 32 (40 %) patients with CHD and obesity of the 1-st degree accordingly. In the group of patients with obesity of the 2-nd degree the following frequency distribution of alleles and genotypes of leptin gene polymorphism (Arg223Gln) took place: 23 people, that is worth to 32.39 %, were the carriers of A allele, 48 patients (67,61 %) – G allele; 13 (18,31 %), 24 (33,80 %) and 34 (47,89 %) respectively had A/A, G/A and G/G genotypes. In the group of patients with combined CAD and obesity of the 3-d degree 16 patients (22,54 %) were carriers of A allele: 55 people (of 77.46 %) - G allele; 8 (11,28 %), 25 (35,2 %) and 38 (of 53.52 %) – A/A, G/A and G/G genotypes, respectively.

17,46 % and 9,85 % more patients with CHD and obesity of the 3-d degree were carriers of the G allele in comparison with patients of the groups 1 and 2, as A allele , conversely, was more common in individuals with obesity of the 1-st and 2-nd degree. G/G Genotype was significantly more prevalent in patients with coronary artery disease and obesity of the 3-d degree on 13.52 % and 5,63 %, and A/A genotype – less on 11.22 % of 7.03 %, compared to patients with obesity 1-st and 2-nd degree, respectively.

Table 2

Frequency of alleles and genotypes of leptin gene polymorphism (Arg223Gln) depending on BMI in patients with CHD and obesity

Genetic markers group 1	group 1 Obesity of the 1-st degree (n = 80)	group 2 Obesity of the 2-nd degree (n = 71)	group 3 Obesity of the 3-d degree (n = 71)
Allele A	32 (40 %)	23 (32,39 %)*	16 (22,54 %)*#
Allele G	48 (60 %)	48 (67,61 %)*	55 (77,46 %)*#
Genotype A/A	18 (22,5 %)	13 (18,31 %)	8 (11,28 %)*
Genotype G/A	30 (37,5 %)	24 (33,80 %)	25 (35,2 %)
Genotype G/G	32 (40 %)	34 (47,89 %)*	38 (53,52 %)*#

Thus, G allele and G/G genotype of the leptin gene polymorphism of (Arg223Gln) are more common among the patients with coronary artery disease and obesity, and the frequency of their detection increases with the growth of BMI in the Ukrainian population.

These data match the results obtained by V. S. Mattevi et al. in 2002 [4] in the Brazilian population, A. Portoles et al in 2006 [5] in the Spanish population, Y. Y. Yako in 2012. [6] among the people of Africa, proves, that the carriage of this genotype is associated with the development of obesity. However, in the studies of T. Gotoda et al [7] in the British population, A. Constantin et al. [8] and the results of the meta-analysis, performed by

M. Neo et al. [9] in romanes, these linkages were not obtained. Moreover, N. Yiannakouris et al. in 2001 found that homozygote is more dominant than 223 R allele among people with normal body weight significantly than in patients with overweight and obesity [10]. Research results are contradictory and require further research.

CONCLUSIONS

G allele and G/G genotype of leptin gene polymorphism (Arg223Gln) were associated with the development of obesity in CHD patients, and the frequency of their detection increases with the growth of BMI in the Ukrainian population.

PROSPECTS FOR FUTURE STUDIES

Given the urgency of the comorbid pathology problem further research should be directed towards the study of other associations of gene polymorphisms with the development and progression of cardiovascular diseases and obesity.

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