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RELATIONSHIP OF FV (LEIDEN) AND FII (PROTHROMBIN) GENE MUTATIONS WITH CONTROLLABLE RISK FACTORS IN PATIENTS WITH CORONARY HEART DISEASE

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Abstract:

Currently, a large number of studies are devoted to the study of polymorphisms of various genes in patients with coronary heart disease (CHD). The study of some of them, for example, genes of the blood coagulation system, has revealed some contradictions or vice versa patterns and deserves further consideration.

Keywords: G1691A mutation of gene V (F5), Arg506Gln mutation of gene II (F2), coagulation factors of blood coagulation system, ischemic heart disease, prevention

It is quite common in clinical practice to meet patients with marked atherosclerosis, but myocardial infarction does not develop. To date, the world scientific base has enough data on risk factors of myocardial infarction, but their significance in representatives of different nationalities, of course, has not yet been fully studied. Polymorphic markers of endothelin-1 gene, endothelial nitric oxide synthetase type 3, ACE inhibitor, fibrinogen, glycoprotein receptors of platelets, lipoprotein lipase and others are among the actively studied genetic factors of CHD. One of the most studied and controversial polymorphisms according to Shevchenko A.V. (2010), is a single nucleotide substitution C677T in the gene MTHFR. According to Nicolaes G.A. (2002), Dankovtseva E.N. (2006), the propensity to venous thrombosis is associated with the carrier of factor V-Leiden. According to clinical and genealogical analysis in women, the combination of factor V mutation with obesity, hyperlipidemia or diabetes mellitus increased the risk of MI by 25 times, and in smoking women by 32 times. According to the Health Professionals Follow-up Study, Physicians Health Study (Western Europe), EatSmart (Australia), a preventive program for CHD patients, aimed at the family, showed the association of nutrition, diet, obesity, reduction of cholesterol (CH) in the blood with coagulation and fibrinolytic properties of the blood and their association with the risk of death from CHD, in turn, the data obtained in the study based on endpoints showed a 52% reduction in the development of the risk of sudden death in CHD and arterial hypertension.

Hereditary variations of proteins involved in the formation of coagulation balance (methylenetetrahydrofolate reductase (MTHFR), Leiden mutation and others), studied in scientific studies GISSI-2 (Italy) and HSDS (Helsinki Sudden Death Study), as well as English, Japanese, Kazakh, Caucasian populations, showed their contribution to the early manifestation of CHD in patients under 40-50 years old. Recently, markers not directly related to lipid metabolism have attracted increasing attention as potential markers. Coagulation factor or clotting factor V is a protein cofactor in the formation of thrombin from prothrombin. Several functionally significant mutations have been identified in the gene encoding FV, of which the most frequent in different populations is the G1691A mutation (which in the protein structure corresponds to the amino acid substitution of Arg (R) for Gln (Q) at position 506), also known as the "Leiden mutation", designated by some authors as an indicator of the risk of venous thrombosis [4,8]. A change in the structure of this gene confers resistance to coagulation factor V, its degradation is slowed down, resulting in hypercoagulability. The risk of thrombosis formation increases. Phenotypically, the Leiden mutation manifests itself as a dominant trait, i.e. its damaging effect is realized even in the presence of one copy of the damaged gene [6]. Mutation G20210A of the prothrombin gene or clotting factor II - leads to overproduction of prothrombin and increased blood clotting. It is inherited in an autosomal dominant pattern and occurs even in heterozygotes. The G/A genotype is a risk indicator for thrombosis and myocardial infarction. In the occurrence of thrombosis, the 20210A mutation is often found in combination with the Leiden mutation [8].

OBJECTIVE To determine for the first time in patients with stable angina pectoris of Uzbek ethnicity the prevalence of FV (Leiden) and FII (prothrombin) gene mutations as hypercoagulation factors and their association with CHD risk factors.

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MATERIALS AND METHODS

The material for this study was venous blood from the ulnar vein in the volume of 1 ml. Genomic DNA was isolated from peripheral blood lymphocytes using a reagent kit for DNA isolation - Diatom™ DNA Prep 200 (Izogen LLC, Moscow, Russia). The DNA supernatant was genotyped by PCR-amplification, PCR-analysis was performed using PCR-amplification kits with primer pairs for detection of the studied polymorphic states of FV and FII genes. Statistical processing of the obtained results was performed using standard programs from the analysis package (data analysis kit "Microsoft Exsel-2007") and using the indicators of evidence-based medicine.

RESULTS AND DISCUSSION

The existence of genetic predisposition to the development of thrombosis due to mutations and polymorphic variants of genes has now been proved. Among the most important of them predisposing to the development of venous thrombosis are polymorphisms of plasminogen activator inhibitor type I (PAI-I), mutations of factor II - prothrombin, factor V Leiden, as well as polymorphisms of the MTHFR gene. 28 (93.3%) healthy individuals and 112 (83%) patients with CHD (SSc) were selected for genotyping from 30 and 135 respondents.

Analysis of Ala222Val polymorphism of MTHFR gene revealed significant heterogeneity in frequencies of pathologic and normal genotypes in CHD patients and healthy individuals. Thus, the Val222 allele of the MTHFR gene in homozygous state is not found in patients with CHD, whereas in the group of healthy individuals it is found 3 times more, which respectively makes up 10.7% of the whole sample of control group individuals. The frequency of heterozygous Ala222Val genotype of the MTHFR gene is higher by almost 42% in the group of CHD patients compared to the group of healthy individuals. The highest occurrence of Ala222Ala genotype was observed in the group of healthy individuals in the number of 13 persons (in 46.4% of cases) than in the group of IBS patients of Uzbek nationality. These differences have high statistical significance and are thus of non-random character. In the general population of the globe, the 677T mutation of the MTHFR gene is widespread enough in representatives of the European (Caucasian) race. The frequencies of two major mutations (C677T and A1298C) in the US population were studied [2,7].

Similar results were obtained in our study (77.7%), which allows us to attribute us to the group of European population samples with polymorphism for the 677T mutation of the MTHFR gene [3,7]. Thus, genetic typing of Ala222Val of the MTHFR gene to identify a group of individual FRs will allow timely optimization of primary and secondary prevention of atherosclerosis and atherothrombosis in the population, which will significantly reduce the incidence of SSN in Uzbek nationality. In the occurrence of thrombosis, mutation 20210A is often found in combination with the Leiden mutation. According to our studies, there is no correlation of the pathology under study with the 20210A mutation of the FII gene, whereas there is a rather stable correlation of the 506Gln mutation of the FV gene with CHD, which also creates conditions predisposing to increased thrombosis in carriers of this mutation.

Analysis of more than ten independent studies has shown that among patients with Leiden mutation the average risk of myocardial infarction increases by 1.5 times. Moreover, the Leiden mutation leads to a 2.8-fold increase in the number of patients without significant coronary stenosis who develop myocardial infarction [4,5,8].

In this connection, the prevalence of FV (Leiden) and FII gene mutations as factors of hypercoagulability in IBS patients of Uzbek nationality was determined for the first time. In the IBS group, 23 respondents (20.5%) were carriers of the 20210A mutation of the FII gene, whereas 35 people became reliable carriers of the 506Gln mutation of the FV gene, which amounted to 31.3% ($P<0.05$). Apparently, the low prevalence of this mutation probably will not be a fundamental factor in the risk of thrombosis and subsequently MI in 24 healthy individuals (85.7%) of young age, but it will certainly play its role in 23 patients (20.5%) with CHD (SSc) who participated in our study.

According to scientific data the presence of Leiden mutation increases the risk of myocardial infarction fivefold, if the patient, besides Leiden mutation of factor V, also has mutation 20210A of FII gene. And an increased risk of myocardial infarction in patients with the 20210A genotype (of the FII gene) was found in individuals younger than 51 years of age [6]. In confirmation of these data, only one (3,4%) of our examined patients at the age of 31 years with CHD and presence of hereditary aggravation has mutation of both genes FV (Leiden) and FII, which according to clinical and anamnestic data may have determined early development of angina pectoris and high frequency of angina attacks in this patient.

Smoking in the presence of 20210A genotype increases the risk of myocardial infarction more than 40 times [6]. Genetic analysis of a group of patients with first myocardial infarction (age 18-44 years) in the Netherlands showed that the 20210A variant occurs

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four times more often in comparison with the healthy group, which corresponds to a 4-fold increase in the risk of infarction [1]. It is possible that this complication may occur in a single (3.8%) healthy smoker aged 26 years with hereditary aggravation of the 20210A genotype. Today it is already known that the risk of severe angina pectoris is directly proportional to the number of detected genetic abnormalities. This hypothesis is confirmed by the presence of clinical debut of CHD in our patients (r=0.20), which was reflected in the number of ambulance calls per year in these individuals 1.67±0.15 calls on average from the number of examined respondents.

The obtained data raise the question about the necessity to continue the research in the chosen direction. The occurrence of FV (Leiden) and FII gene mutations in patients with stable angina pectoris of Uzbek ethnicity, as factors of hypercoagulability, turned out to be much lower than the data of the scientific studies known so far. In this regard, the study of the association of polymorphisms of these genes with the development and course of the above pathology will allow us to assess the risk of developing life-threatening conditions, as well as to correctly determine the methods of their treatment and the possibility of using certain drugs.

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