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ARAŞTIRMA / RESEARCH

New genetic risk factors for myocardial infarction at young patients in Southern Turkey

Türkiye'nin güneyinde genç hastalarda görülen miyokart enfarktüsü için yeni genetik risk faktörleri

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Abstract

Purpose: Genetic predisposition plays an important role in the development of atherosclerosis in young patients. The aim of this study was to determine the relationship between myocardial infarction and HLA antigens in young patients who had myocardial infarction in southern region of Turkey.

Materials and Methods: We enrolled 50 patients (36 male, 14 female, mean age 45.0 ± 7.1) who had myocardial infarction before 45 years old in men and 55 years old in women and 50 healthy subjects (31 male, 19 female, mean age 51.5 ± 5.5) as a control group into the study. Venous blood samples were collected for HLA tissue typing and determining trombogenic factors. Histocompatibility antigens (HLA-A,B,C,-DQ,-DR) were studied with Polymerase Chain Reaction (PCR)-Sequance Spesific Oligonucleotide typing (SSO) method.

Results: Frequency of HLA antigens in patients and controls were 38% and 10% for HLA-A24, 40% and 10% for HLA-DQB2, 26% and 6% for HLA-DRB1-7 and 52% and 26% for HLA-DRB4-1. Chi square test revealed a significant relation with the disease and the presence of these antigens. In the logistic regression analysis, smoking, Lp(a), homocysteine and HLA-DQB1 subtype were independently associated with development of MI in young patients.

Conclusion: The presence of HLA-A24, HLA-DQB2, HLA-DRB1-7 and HLA-DRB4-1 may be used as genetic markers for the tendency to coronary artery disease in southern region of Turkey.

Keywords:. Myocardial infarction, genetic risk factors, HLA antigens

Öz

Amaç: Genetik yatkınlık genç hastalarda ateroskleroz gelişiminde önemli rol oynamaktadır. Bu çalışmanın amacı, Çukurova bölgesinde miyokart enfarktüsü geçiren genç hastalarda miyokart enfarktüsü ile HLA antijenleri arasındaki ilişkiyi belirlemektir.

Gereç ve Yöntem: Çalışmaya 45 yaşından önce miyokart enfarktüsü geçirmiş 36 erkek ve 55 yaşından önce miyokart enfarktüsü geçirmiş 14 kadın olmak üzere (ort. yaş 45.0±7.1) toplam 50 hasta alındı. Kontrol grubu 50 sağlıklı bireyden (31 erkek, 19 kadın, ort. yaş 51.5±5.5) oluşturuldu. HLA doku tiplemesi ve trombojenik faktörlerin belirlenmesi için venöz kan örnekleri toplandı. HLA antijenleri (HLA-A,B,C,-DQ,-DR) Polimeraz Zincir Reaksiyonu- Sekans Spesifik Oligonükleotit tiplendirme (PCR-SSO) metodu ile çalışıldı.

Bulgular: Hasta ve kontrol grubunda HLA antijenlerinin sıklığı HLA-A24 için %38 ve %10, HLA-DQB2 için %40 ve %10, HLA-DRB1-7 için %26 ve %6 ve HLA-DRB4-1için %52 ve %26 idi. Ki-kare testi hastalıkla ve bu antijenlerin varlığı arasında anlamlı bir ilişki olduğunu ortaya koydu. Lojistik regresyon analizinde sigara kullanımı, Lp(a), homosistein ve HLA-DQB1 alt tipi genç hastalarda MI gelişimi ile bağımsız olarak ilişkiliydi.

Sonuç: Çalışma sonuçlarına göre HLA-A24, HLA-DQB2, HLA-DRB1-7 ve HLA-DRB4-1 antijenlerinin Çukurova bölgesinde koroner arter hastalığına eğilimi belirlemede genetik belirteçler olarak kullanılabileceği sonucuna varılmıştır.

Anahtar kelimeler: Miyokart enfarktüsü, genetik risk faktörleri, HLA antijenleri

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INTRODUCTION

Coronary artery disease (CAD) is the leading cause of death in the world. It is most commonly caused by atherosclerosis which is a chronic inflammatory disease of arterial intima and characterized by the formation of atherosclerotic plaque[1]. CAD has a complex etiology, mainly a combination of traditional risk factors and genetic predisposition. Major risk factors that cause the disease have been identified with large epidemiological studies. Hypertension, dyslipoproteinemia, diabetes mellitus, and smoking are among the known risk factors of coronary atherosclerosis. However these traditional factors are not sufficient to identify high risk asymptomatic individuals and can not explain all cases of CAD. Genetic predisposition is an important and non modifiable risk factor and is becoming increasingly important. In fact, the hereditary effect on CAD can account for almost 40 to 50% of cases[2,3]. Understanding the genetic basis can contribute improving the management and prevention of CAD.

Recently, CAD is considered as a disease with significant genetic origin and affected by many factors[4]. Significant amount of T-lymphocytes have been shown in early fatty lesions and advanced fibrous plaques at histopathological studies. This observation and some studies suggest that human leukocyte antigens (HLA) would be useful in determining the genetic tendency to coronary artery disease[5,6].

Early detection of CAD may provide earlier intervention for genetically sensitive individuals. However, knowledge of genetic CAD susceptibility is important in providing risk information and guiding decision making but it is not effective in preventing clinical events. Further research that investigates outcomes regarding genetic risk assessment for CAD is necessary. Detection of individuals with genetic predisposition and effective treatment of additional risk factors may also be useful in the prevention of myocardial infarction. The aim of this study is to investigate the association between myocardial infarction at young age (male <45 years, female <55 years) and known and some new risk factors of CAD that may reflect genetic predisposition such as HLA antigens in the southern region (Çukurova region) of Turkey.

MATERIALS AND METHODS

Fifty patients (36 men with the history of myocardial infarction before the age of 45 and 14 women with the history of myocardial infarction before the age of 55) and 50 healthy individuals with no history of CAD (31 male and 19 female) as a control group were included in this study. Control subjects were selected from healthy individuals without history of cardiovascular disease, cancer, chronic obstructive pulmonary disease and hepatitis. All participants were informed about the study and their written consent was obtained.

Patients included in this study were examined for classic CAD risk factors like age, gender, hypertension, diabetes, lipid profile, smoking, family history and the presence of HLA antigens. All patients and control group were subjected to a detailed history and physical examination. For the determination of HLA antigens (HLA-A,B,C,-DQB1,-DR1,-DRB3,4,5 sub groups) blood samples taken from the median cubital vein into EDTA added tubes were kept at -20 °C before the evaluation. After DNA isolation (Vivantis Inc. GF-1 Blood DNA Extraction Kit), HLA allele determination was performed with Luminex brand device (Luminex-200) by using PCR-sequance spesific oligonucleotide typing (SSO) method at Cukurova University Medical Faculty Central Laboratory. The study was approved by Çukurova University Faculty of Medicine ethics committee.

Statistical analysis

SPSS software (PASW, version 17.0, SPSS, Chicago, Illinois) was used for statistical analysis. Categorical data were presented as number and percentage; continuous data were presented as mean and standard deviation (median and minimum - maximum if necessary). Chi-Square test statistic was used to compare categorical data between the two groups. Independent samples t test was used with normal distributed continous data and Mann-Whitney U test was used with not normal distributed continous data. Binary logistic regression analysis was used to identify the relationship between dependent and independent variables using the least number of variables. Statistical significance level (p) was <0.05 for all tests.

RESULTS

Table 1 shows the clinical characteristics of the patients included in this study. There was no significant difference in sex distribution between the groups (p> 0.05). There was significant difference between the age of two groups. But this difference is because the control group was chosen from healthy male over the age of 45 and healthy female over the age of 55 in order to exclude patients with possibility of having an early miyocardial infarction.

Table 1. The clinical data of the patient and control groups

	Patient	Control	P
Age (years)	45.0±7.1	51.5±5.5	*
Gender (male / female, n)	36/14	31/19	NS
Hypertension (n)	23	0	**
Diabetes mellitus (n)	14	0	**
Cigarette (n)	35	9	0.0001
Family history (n)	32	17	0.005
LDL-C (mg/dl)	106.8±36.6	117.0±27.1	NS
HDL-C (mg/dl)	41.26±10.0	41.5±6.9	NS
TRG (mg/dl)	161.4±89.8	131.7±62.4	NS
T-Cho (mg/dl)	187.4±68.8	187.5±30.5	NS

T-Cho: Total cholesterol, LDL-C: low-density lipoprotein cholesterol, HDL-C: high-density lipoprotein cholesterol, TRG: Triglyceride, NS: Non Significant; * There was significant difference between the age of two groups. But this difference is because the control group were chosen from healthy male over the age of 45 and healthy female over the age of 55 in order to exclude patients with possibility of having an early miyocardial infarction.; ** Because there was no hypertension and diabetes in control group, no comparison have been made between two groups in terms of these two parameters. In the patients group 23 patients (46%) had hypertension and 14 (28%) had diabetes.

Table 2. HLA-A alleles detected at patients and controls

HLA-A alleles	Patients		Controls		P
	n	%	n	%	
A1	5	10	10	20	NS
A2	19	38	13	26	NS
A3	10	20	9	18	NS
A11	9	18	14	28	NS
A23	2	4	5	10	NS
A24	19	38	5	10	0.002
A26	5	10	7	14	NS
A29	2	4	3	6	NS
A30	4	8	5	10	NS
A31	3	6	1	2	NS
A32	3	6	8	16	NS
A33	5	10	0	0	0.056
A66	1	2	0	0	NS
A68	6	12	11	22	NS
A69	1	2	1	2	NS

Smoking was significantly higher in the patient group (p <0.05). The number of smokers were 35 (70%) in the patient group and 9 (18%) in the control group. Family history of CAD was significantly higher in the patient group (p <0.05). The number of those who have a family history of CAD were 32 (64%) in the patient group and 17 (34%) in the control group. Lipid parameters (T-Chol, HDL, LDL and TRG) did not differ between the groups (p> 0.05)

HLA-A24 was higher in the patient group (p <0.05). The number of those who have HLA-A24 were 19 (38%) in the patient group and 5 (10%) in the control group. HLA-A33 allele was higher in the patient group, but there was no statistically significance (p =

0.056). HLA-A33 allele was present at 5 (10%) subjects in the patient group, whereas in the control this allele was not detected. Other HLA-A alleles showed similar distribution between the two groups (Table 2).

Table 3. HLA-B alleles detected at patients and controls

HLA-B alleles	Patients n	%	Controls n	%	P
B7	3	6	4	8	NS
B8	4	8	1	2	NS
B13	5	10	3	6	NS
B14	3	6	0	0	NS
B15	2	4	5	10	NS
B18	1	26	9	18	NS
B27	2	4	4	8	NS
B35	1	34	23	46	NS
B37	1	2	0	0	NS
B38	1	2	5	10	NS
B39	2	4	0	0	NS
B40	2	4	6	12	NS
B41	2	4	1	2	NS
B42	0	0	1	2	NS
B44	12	24	8	16	NS
B48	1	2	0	0	NS
B49	1	2	2	4	NS
B50	5	10	0	0	0.056
B51	8	16	8	16	NS
B52	5	10	6	12	NS
B53	1	2	1	2	NS
B55	2	4	1	2	NS
B58	2	4	2	4	NS

There was no significant difference at HLA-C alleles between the two groups (Table 4).

Table 4. HLA-C alleles at patients and controls

HLA-C alleles	Patients n	%	Controls n	%	P
C1	1	2	0	0	NS
C2	1	2	3	6	NS
C3	5	10	2	4	NS
C4	18	36	25	50	NS
C5	8	16	8	16	NS
C6	11	22	5	10	NS
C7	11	22	12	24	NS
C8	2	4	0	0	NS
C12	20	40	16	32	NS
C14	4	8	5	10	NS
C15	5	10	5	10	NS
C16	6	12	3	6	NS
C17	2	4	2	4	NS

HLA-B50 allele was higher in the patient group, but there was no statistically significance (p = 0.056). HLA-B50 allele was present at 5 (10%) subjects in the patient group, whereas in the control this allele was not detected. Other HLA-B alleles showed similar distribution between the two groups (Table 3).HLA-DQB2 was significantly higher in the patient group (p <0.05). The number of those who have HLA-DQB2 were 20 (40%) in the patient group and 5 (10%) in the control group. Other HLA-DQB alleles showed similar distribution between the two groups (Table 5).

Table 5. HLA-DQB alleles at patients and controls

HLA-DQB alleles	Patients n	%	Controls n	%	P
DQB2	20	40	5	10	0,001
DQB3	33	66	29	58	NS
DQB4	0	0	3	6	NS
DQB5	18	36	17	34	NS
DQB6	12	24	20	40	NS

HLA-DRB1-7 and DRB4-1 were significantly higher in the patient group (p <0.05). HLA-DRB1-7 allele was present at 13 (26%) subjects in the patient group and 3 (6%) in the control group. HLA-DRB4-1 was detected at 26 (52%) in the patient group and 13 (26%) in the control group. HLA-DRB1-10 was higher in the control group (p <0.05). HLA-DRB1-10 was detected at 6 (12%) in the control group whereas it has not been observed in patient group.

Table 6. HLA-DRB alleles at patients and controls

HLA DRB alleles	Patients n	%	Controls n	%	P
DRB1-1	4	8	3	6	NS
DRB1-3	6	12	6	12	NS
DRB1-4	12	24	7	14	NS
DRB1-7	13	26	3	6	0,012
DRB1-8	2	4	1	2	NS
DRB1-9	1	2	2	4	NS
DRB1-10	0	0	6	12	0,027
DRB1-11	25	50	25	50	NS
DRB1-12	2	4	1	2	NS
DRB1-13	6	12	9	18	NS
DRB1-14	7	14	8	16	NS
DRB1-15	8	16	13	26	NS
DRB1-16	7	14	3	6	NS
DRB3-1	3	6	7	14	NS
DRB3-2	30	60	26	52	NS
DRB3-3	2	4	2	4	NS
DRB4-1	26	52	13	26	0,013
DRB5-1	6	12	4	8	NS
DRB5-2	6	12	2	4	NS

Other HLA-DRB alleles showed similar distribution between the two groups (Table 6). Table 7 shows the

HLA alleles which have statistically significance between the two groups.

Table 7. Statistically significant HLA antigens

HLA antigens	Patients n	%	Controls n	%	P
A24	19	38	5	10	0.002
A33	5	10	0	0	0.056
B50	5	10	0	0	0.056
DQB2	20	40	5	10	0.001
DRB1-7	13	26	3	6	0.012
DRB1-10	0	0	6	12	0.027
DRB4-1	26	52	13	26	0.013

We have performed logistic regression analysis to determine the independent association of the risk factors with myocardial infarction occurrence in young patients. In the logistic regression analysis, smoking (OR=10.882 [2.741-43.198 in 95 % CI]; p=0.01), Lp (a) (OR=1.023 [1.004-1.042 in 95 % CI], p=0.018), homocysteine (OR=1.306 [1.150-1.482 in 95 % CI]; p<0.001) and HLA-DQB1 subtype (OR=5.821 [1.289-26.283 in 95 % CI]; p=0.022) were independently associated with MI occurrence in young patients.

DISCUSSION

Important information about the basics of the development of atherosclerosis has been reached. But, precise information could not still be obtained about who gets which clinical form of atherosclerosis, and about how to stop it. CAD is one of the most important clinical forms of atherosclerosis. It has significant effect on the health of individuals and society. Various factors related with the initiation and progression of CAD have been detected[7]. However, in some patients, the absence of any conventional risk factors, has led to the search for new risk factors. In this study, we aimed to examine the role of classical risk factors and histocompatibility antigens to determine tendency to CAD.

HLA antigens are polymorphic molecules involved in antigen presentation and encoded by genes located in the MHC complex on chromosome 6. Associations between HLA type and autoimmune diseases, such as systemic lupus erythematosus (SLE), diabetes (type 1) and rheumatoid arthritis, are well established but the potential association of genetic variation affecting antigen presentation with cardiovascular disease has not been systematically investigated in large groups. The importance of such studies is stressed by recent experimental findings of an involvement of autoimmunity in the atherosclerotic disease process. In addition to the classic risk factors, in our study we aimed to investigate the relationship between HLA antigens and CAD. The Important role of inflammation in the development of coronary atherosclerosis was shown in 1966 by Constantinides with intense inflammation and macrophage infiltration at histological samples of plaques[8]. A variety of inflammation cells, activated T lymphocytes, CD4 - CD8 lymphocytes and class II histocompatibility antigens on these lymphocytes were found at early atherosclerotic lesion formation as well as advanced plaques[9]. Immune or possible autoimmune response can be thought to have a role in the etiology of atherosclerosis.

In this study, tissue antigens, HLA-A24, -DQB2, -DRB1, -DRB4-1 and –DRB1-7 were significantly correlated with myocardial infarction. It is noteworthy that 3 of histocompatibility antigens associated with myocardial infarction (-DQB2, -DRB1 and -DRB4-1-7) were class II. Class II antigens have a role in the majority of the diseases associated with HLA[10]. Class II antigens identifies foreign antigens to CD4 T-lymphocytes. Normally they are present on the surface of macrophages, B cells and activated T cells. However, at pathological conditions such as atherosclerosis they can be found in endothelial cells and vascular smooth muscle cells[11,12]. This condition is called aberrant expression. With the aberrant expression, tissue antigens triggers autoimmune response by acting as a foreign antigen. In atherosclerotic plaques, T cells and expression of class II antigens at their surface have been shown to be activated[13,14]. Presence of activated T cells and expression of class II antigens at their surface has been proven by pathology studies[9,15]. DR and-DQ antigens were observed at atherosclerotic plaques of patients with or without previous myocardial infarction. Lymphocytes that have this antigen were found to be more intensely collected in cracked area of plaque or where there is significant inflammation[15,16]. These findings support the role of activated T-lymphocytes and chronic inflammation in the etiology of myocardial infarction. One of the investigations about the role of MHC class II molecules in human atherosclerosis is the study of Swanberg et al.[17]. This study demonstrated that a mutation in the promoter of the MHC II transactivator gene leading to a reduced expression of MHC class II molecules on activated leucocytes has been linked to increased susceptibility to acute

myocardial infarction (AMI). This observation of a relation between HLA types and AMI add some additional support for a clinically important role of autoimmunity in cardiovascular disease. In our study, association of 3 antigens of DRB, DQB subtypes with myocardial infarction is consistent with these observations. Several studies also previously were addressed in relatively small groups and the results showed inconsistency about the possible relation between HLA and cardiovascular disease[18]. Palikhe et al showed in their study that HLA-DRB1*01 was associated with the presence of severe coronary disease (OR 2.4), suggesting that HLA type affects cardiovascular risk19. Björkbacka et al. demonstrated a weak association between HLA-DRB1 and DQA1 loci and cardiovascular disease20. While Stone and colleagues detected a significant relationship between myocardial infarction and HLA-B38, results of Logan, Scott and his colleagues did not support these findings[21-23]. Khaitov and colleagues found a significant correlation between CAD and HLA-B12 -DR1 -DR4[24]. These results are partially similar to our findings. Balliuzek and friends found a significant relationship between CAD and -A2, -B7, -B14, -B15 and-CW4, but the study of Sewdarsen, Jonasson et al failed to show any relationship[25,26]. In terms of association of histocompatibility antigens with myocardial infarction, in our study group, there was no complete analogy with other studies. This situation can be explained by differences on incidence of these antigens by race and geographic regions[27].

Despite all these study results the relationship between HLA subtypes and coronary artery disease is not as strong as in other well established autoimmune involvement such as type 1 diabetes, rheumatoid arthritis, multiple sclerosis, SLE and Crohn's disease. This may be due to a less important role for autoimmunity in cardiovascular disease or because autoimmunity in cardiovascular disease involves several autoantigens presented by variety of different HLA molecules.

In our country, the most common tissue antigens are -A2,-A9,-B35,-CW4,-DR2 and-DR4, while the least common tissue antigens are -A23, -A29, -B15 and -B39[6]. In our cases, -A2,-A24,-B35,-C12,-DQB3 and DRB3-2 alleles were the most commonly detected, and A33,-A66,-B14,-B37,-B39,-C1,-DQB4 and-DRB1-10 alleles were the least commonly detected. These findings can be explained by ethnic and geographic differences as mentioned above.

Classic risk factors such as smoking and positive family history of CAD were found to be significantly correlated with CAD. High rate of smoking in young myocardial infarction patients has been shown by many studies and have been reported in approximately 76-90%[28]. In our study, 35 subjects (70%) in patient group and 9 (18%) subjects in the control group had been identified smoking. Smoking has been associated with increased fibrinogen levels, increased platelet aggregation, impaired fibrinolytic activity, increased vasospasm and reduced coronary flow[29-31]. The negative effects of smoking on early atherosclerosis and plaque instability has been shown. Especially in young patients, smoking was shown to trigger coronary artery spasm and thrombus formation at normal coronary arteries or at minimal atherosclerotic lesions[32]. Also those who continue to smoke after infarction have been reported to have worse results of long-term mortality[33]. Our results were compatible with the literature. Smoking is the leading preventable cause of mortality and not only at atherosclerotic process, role of smoking at spasmogenic and thrombotic burden should not be ignored.

Relationship between CAD and family history of early onset coronary heart disease at first-degree relatives have been shown in many studies. This high risk continues even after adjusting for other risk factors[34]. History of premature CAD at father or other male first-degree relatives before the age of 55, mother or other first-degree female relatives before the age of 65 have shown to increase the risk of developing atherosclerosis 1.3-1.6-fold[35-37]. The predictive value of family history increases as the number of early onset CAD increases and as development age of CAD decreases[38]. Williams and colleagues on their examination of families with a history of early coronary heart disease have shown that only 10% of families did not have the appropriate risk factor[39]. In our study, a positive family history of young age myocardial infarction has been identified as a risk factor.

Traditional risk factors known to be effective in the formation of coronary atherosclerosis; could explain less than 50% of the known changes at the pathogenesis, prevalence and intensity of CAD[40].

In conclusion, in our study, as a preliminary study, new cardiovascular risk factors such as HLA-A33 and HLA-B50 tissue antigens were found to be associated with a slightly increased risk of developing myocardial infarction, but there was no statistical

significance. HLA-DRB1-10 allele was thought to be a protective factor for CAD because it was found only in the control group. Other tissue antigens like HLA-A24,-DQB2,-DRB1-7 and DRB4-1 were found to increase the risk of myocardial infarction. If these findings are supported by subsequent studies, individuals who has tendency to myocardial infarction can be identified and early preventive treatment can be used in southern region of Turkey. Although the results obtained in this study are very limited, this region may be informative for the whole country because it receives substantially immigration from other regions of the country.

Small number of patients in the study group can be seen as the most important limitation. Our study group consists of the limited number of patients because determination of tissue groups is an expensive investigation. Therefore, our findings must be supported by a larger patient groups. Histocompatibility antigens should be examined in patients with early onset myocardial infarction because of rapid development of atherosclerosis. In patients with a history of myocardial infarction and with no known risk factors for CAD tissue group antigens should be investigated for the evaluation of genetic predisposition

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