ORIGINAL ARTICLE

Analysis of thrombophilic gene mutations in coronary artery ectasia

Koroner arter ektazisinde trombofilik gen mutasyon analizi

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ABSTRACT

Objective: Coronary artery ectasia (CAE) is defined as localized or diffuse dilatation in the coronary artery lumen of at least 1.5 times the diameter of adjacent healthy reference segments. The etiology of CAE is still unknown, but the most likely cause is atherosclerosis. The aim of this study was to evaluate several gene polymorphisms that are thought to have an effect on the development of coronary atherosclerosis and have been shown to cause thrombophilia in CAE patients.

Methods: The factor V Leiden (G1691A), factor V H1299R, prothrombin G20210A, factor XIII V34L, beta-fibrinogen-455 G>A, plasminogen activator inhibitor (PAI)-1 4G/5G, and methylenetetrahydrofolate reductase (MTHFR) C677T, and MTHFR A1298C polymorphisms were evaluated in 66 patients with CAE and 32 individuals with normal coronary arteries.

Results: Comparison of the CAE and control groups revealed that the clinical features and the frequency of polymorphism in the thrombophilic genes were similar in both groups. However, when heterozygous and/or homozygous polymorphism was compared between groups, it was found that there was a significantly higher finding of thrombophilic gene polymorphism in the CAE group (p=0.023).

Conclusion: Thrombophilic gene polymorphism may be associated with the formation and clinical presentation of CAE.

ÖZET

Amaç: Koroner arter ektazisi (KAE), koroner arterin lümeninin lokalize veya yaygın olarak dilatasyonu olup, sağlıklı komşu damar segment çapının göre en az 1.5 kat dilate olması olarak tanımlanmıştır. KAE'nin etiyolojisi hala tam olarak bilinmemektedir, ancak en olası nedenin ateroskleroz olduğu gösterilmiştir. Bu çalışmada, KAE hastalarında koroner ateroskleroz gelişiminde etkili olduğu düşünülen ve trombofiliye yol açtığı gösterilmiş bazı gen polimorfizmlerini değerlendirmeyi amaçladık.

Yöntemler: Çalışmamızda KAE (n=66) ve kontrol (normal koroner arter) (n=32) grubundaki 98 hastada trombofili genleri olarak bilinen Faktör V Leiden (G1691A), Faktör V H1299R, Protrombin G20210A, Faktör XIII V34L, B-Fibrinojen-455 G> A, PAI-1 4G/5G, MTHFR C677T ve MTHFR A1298C polimorfizmi değerlendirildi.

Bulgular: Gruplar karşılaştırıldığında klinik özellikleri ve trombofilik genlerdeki polimorfizm sıklığı her iki grupta benzer olduğu görüldü. Ancak, gruplar arasında heterozigot ve/veya homozigot polimorfizmi olup olmayanlar karşılaştırıldığında, KAE grubunda trombofilik gen polimorfizm olanlar anlamlı olarak daha fazla görüldü (p=0.023).

Sonuç: Trombofilik gen polimorfizmi, KAE oluşumu ve klinik görünümü ile ilişkili olabilir.

Cardiovascular disease (CVD) is the leading cause of death around the world. Among CVDs, coronary artery disease (CAD) is the most common, usually presenting as stenotic coronary arteries due to atherosclerosis. In contrast to CAD, coronary artery ectasia (CAE) is characterized by 1.5 times greater localized or diffuse dilatation of the coronary artery lumen compared with the diameter of adjacent healthy

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reference segments. It is a rare phenomenon; the incidence ranges from 1% to 5% in patients undergoing angiography. The presentation of CAE patients varies from asymptomatic to angina and acute myocardial infarction.[1,2]

Abbreviations:

ACE	*Angiotensin I-converting enzyme*
CAD	*Coronary artery disease*
CAE	*Coronary artery ectasia*
CVD	*Cardiovascular disease*
eNOS	*Endothelial nitric oxide synthase*
PCR	*Polymerase chain reaction*
PAI	*Plasminogen activator inhibitor*
MTHFR	*Methylenetetrahydrofolate reductase*

Most cases of CAE are considered a variant of CAD. Although the pathogenesis of CAE is not completely understood, it is likely to involve the destruction of the arterial media, increased wall stress, thinning of the arterial wall, and progressive dilatation of the coronary artery segment. In addition, CAE is also reported to be associated with increased plasma levels of inflammatory markers, cytokines, and oxidative stress.[3] Gene polymorphism studies have indicated a role in CAE.[3–5] However, the pathogenic mechanisms underlying CAE are not yet fully understood, and no effective means of therapy is available for CAE.

Thrombophilia, also referred to as a hypercoagulable state, encompasses a group of inherited or acquired conditions that are associated with an increased risk for thrombosis. The primary hypercoagulable abnormality is linked to specific coagulation proteins that induce a prothrombotic state. Most of these disorders involve inherited mutations and polymorphisms that lead to either a deficiency of a physiologic antithrombotic factor or an increased level of a prothrombotic factor. Secondary hypercoagulable states are diverse (such as aging, oral contraceptive use, hormone replacement therapy, pregnancy, cancer, infection, trauma, surgery) and are mostly acquired disorders that predispose patients to thrombosis through complex, multifactorial, pathophysiological mechanisms.[6] A tendency for thrombosis in CAE patients is known, but the pathophysiological mechanism is unclear.

CAE likely represents an exaggerated form of expansive vascular remodeling in response to atherosclerotic plaque growth, with atherosclerosis being the most common cause. However, while it was first described more than 5 decades ago, management and the etiology are still debated. In the present study, several common thrombophilic gene polymorphisms that are thought to have an effect on the development of coronary atherosclerotic events were evaluated in patients with CAE and in healthy controls.

METHODS

Design and subjects

This retrospective observational study consisted of 66 patients with CAE and 32 subjects with normal coronary arteries. The study was conducted in the Medical Genetics and Cardiology Department of Afyonkarahisar Health Sciences University. The study was approved by the local ethics committee (2014-282) and all participating individuals provided written, informed consent. All of the subjects underwent DNA analysis for the common polymorphisms in thrombophilia genes: heterozygous and/or homozygous polymorphism in genes Factor V (G1691A and H1299R), prothrombin G20210A, factor XIII V34L, beta-fibrinogen-455 G>A, plasminogen activator inhibitor (PAI)-1 4G/5G, and methylenetetrahydrofolate reductase (MTHFR) (C677T and A1298C). Patients with CAE were compared with a control group in terms of polymorphism in any of the thrombophilia genes (heterozygous and/or homozygous polymorphism). A further comparison was conducted for polymorphism of factor V Leiden (G1691A), factor V H1299R, and prothrombin G20210A, 3 genes which have been associated a higher tendency for thrombosis.[7–13]

Determination of patient groups

The diagnosis of CAE was based on international CAE criteria.[14] Patients with abnormal, irregular, or saccular expansion in any coronary arteries of more than 1.5 times the normal coronary artery were diagnosed with CAE. CAE was divided into 4 types according to the classification described by Markis et al.[1] Type 1 is defined as diffuse involvement in 2 or 3 coronary arteries, Type 2 is diffuse disease in 1 vessel and local disease in another, Type 3 is diffuse ectasia in 1 vessel, and Type 4 is localized or segmental ectasia.

The data were defined as follows: hypertension: blood pressure of ≥140/90 mm Hg and/or use of antihypertensive treatment; dyslipidemia: total cholesterol level of >200 mg/dL or low-density lipoprotein cholesterol level of ≥130 mg/dL, triglyceride level of ≥150 mg/dL, or high-density lipoprotein choles-

terol level of ≤40 mg/dL in males and ≤50 mg/dL in females, and/or use lipid-lowering agents; diabetes mellitus: fasting plasma glucose of 126 mg/dL and/or glucose-lowering treatment. Smokers were defined participants who reported smoking currently and regularly (at least 5 cigarettes per day). Cerebrovascular events were defined as ischemic and hemorrhagic events. Body mass index was calculated as weight in kilograms divided by the square of height in meters.

Patients with pregnancy, Kawasaki disease, Takayasu arteritis, Behçet's disease, systemic inflammatory vasculitis, rheumatoid arthritis, systemic lupus erythematosus, ankylosing spondylitis, Ehler-Danlos syndrome, Marfan syndrome, congenital coronary artery malformations (such as a fistula), and dissection due to known thoracic trauma were all excluded from the study. In addition, cases of malignancy, hyperhomocysteinemia, vitamin B12 and folate deficiency, trauma or surgery, and oral contraceptive use were all excluded.

Control group

The control group consisted of subjects with normal coronary arteries previously assessed by coronary angiography. Indications for coronary angiography in the control group were atypical chest pain, preoperative evaluation, and/or suspected ischemia findings in stress tests. Patients with typical angina or acute coronary syndrome were excluded.

DNA isolation, PCR, and reverse hybridization

Genomic DNA of 98 samples was extracted from fresh blood anticoagulated with ethylenediaminetetraacetic acid using either the Cardiovascular Disease StripAssay lysis solution and GENTRACT resin (ViennaLab Diagnostics GmbH, Vienna, Austria) or the QIAamp DNA blood Midi (Qiagen, Hilden, Germany) extraction kit and a silica membrane-based DNA purification method that can yield up to 60 mg of DNA from 2 mL initial blood volume. The CVD strip assay screens for gene mutations are based on a reverse hybridization principle.

The different target gene sequences were concurrently amplified and biotin-labeled in a single amplification reaction. The reaction consisted of 0.1 mg of DNA added to 15 mL of already prepared polymerase chain reaction (PCR) amplification mix, including primers that flank the target sequences and deoxynucleoside triphosphates in the presence of 1 U Taq polymerase. The PCR cycles were optimized as follows: 2 minutes at 94°C of initial denaturation followed by 35 cycles of amplification (15 seconds denaturation at 94°C, 30 seconds annealing at 58°C, and 30 seconds extension at 72°C), and a final extension of 3 minutes at 72°C. The amplification products were denatured and selectively hybridized to a test strip that contained allele-specific oligonucleotide probes (wild type and mutant) immobilized as an array of parallel lines. Bound biotinylated sequences were detected using streptavidin alkaline phosphatase and color substrates.

Statistical analysis

Statistical analyses were conducted using IBM SPSS Statistics for Windows, Version 22.0 software (IBM Corp., Armonk, NY, USA). The variables were investigated using visual and analytic methods to determine whether or not they were normally distributed. The mean and SD or median and interquartile ranges were used as descriptive statistics. The normality of continuous variables was tested using the one-sample Kolmogorov-Smirnov test. A chi-square test was used to compare nominal and categorical variables (all genes, gender, hypertension, diabetes, smoker, hyperlipidemia). A t-test was used to compare the numerical variables, given that there was normal distribution. In addition, the patient data were analyzed for the presence of polymorphism in the 3 most frequent thrombophilia genes. A p value of <0.05 was considered statistically significant.

RESULTS

Table 1 shows the distribution of patients according to CAE classification. Table 2 summarizes the clinical characteristics of the groups. There were no significant differences between the groups with regard to age, gender, smoking status, or the presence of hyper-

Table 1. Distribution of types of coronary artery ectasia in the study population

Ectasia type	Number of patients	% value
Type 1	12	18
Type 2	12	18
Type 3	15	23
Type 4	27	41

Table 2. Baseline demographic and clinical characteristics of the study group

Variables	CAE (n=66)			Control (n=32)			*p*
	n	%	Mean±SD	n	%	Mean±SD	
Age (years)**			61.2±10.7			61.91±11.23	0.754
Women*	8	12		9	28		0.051
Hypertension*	35	53		14	43		0.389
Diabetes mellitus*	19	29		4	12.5		0.074
Hyperlipidemia)*	21	32		9	28		0.71
Smoker*	21	32		9	28		0.71

* Chi-square test; ** Independent samples t-test; p<0.05 statistical significance. CAE: Coronary artery ectasia; SD: Standard deviation.

Table 3. Genotype and all frequency candidate genes of both groups

Genes	CAE (n=66)	Control (n=32)	*p*
Any thrombophilic gene (n) polymorphism Yes/No	64/2	27/5	0.023*
Any thrombophilic genes (n) (3 most common) Yes/No	14/52	7/25	0.94
Factor V Leiden (G1691A), N/WT/M (n)**	64/2/0	28/4/0	0.067
Factor V H1299R (n)** N/WT/M	56/10/0	27/5/0	0.951
Prothrombin G20210A (n)** N/WT/M	65/1/0	31/1/0	0.597
Beta-fibrinogen-455 G>A(n) N/WT/M	34/24/8	19/13/0	0.121
MTHFR C677T (n) N/WT/M	33/27/6	19/11/2	0.668
MTHFR A1298C (n) N/WT/M	21/35/10	9/19/4	0.879
PAI-1 4G/5G (n) N/WT/M	17/33/16	11/14/7	0.675
Factor III V34L (n) N/WT/M	45/17/4	21/10/1	0.733

*Chi-square test; p<0.05 statistical significance. **Genes were arranged from high to low incidence in thrombophilia.
CAE: Coronary artery ectasia; M: Mutant; N: Normal; WT: Wild type.

tension, diabetes mellitus, or hyperlipidemia.

The CAE and control groups were similar in the frequency of 8 thrombophilia gene polymorphisms (Table 3). However the patients with CAE were more likely to have any of thrombophilic gene polymorphisms than the control group (p=0.023).

DISCUSSION

To the best our knowledge, our study is the first to explore common thrombophilia gene mutations in CAE, with the exception of beta-fibrinogen. The tendency for thrombosis in CAE patients is a concern for every clinician. In our study, the frequency of any mutation in thrombophilia genes was significantly higher in CAE patients than in the control group. The higher frequency of any thrombophilia mutation might be linked to increased susceptibility to thrombosis in CAE. However, all of the patients with CAE in this study also had symptoms of chest pain, which required testing with coronary angiography. Thus, this study group might represent only symptomatic patients with CAE and not the overall CAE population. It would appear that the higher frequency of thrombophilia made these CEA patients become more symptomatic; however, post mortem studies that include asymptomatic CAE patients are needed to support this view.

There are well-known risk factors for CAE: atherosclerosis, smoking, older age, hypertension, diabetes, and hyperlipidemia. There has also been interest in the possibility of genetic susceptibility for CAE; however, genetic studies explaining the formation of CAE are still insufficient. There are also several studies of gene polymorphisms other than thrombophilia in patients with CAE. The angiotensin-I converting enzyme

(ACE) genotype DD polymorphism seems to be a potent risk factor for the development of CAE.[15] Lamblin et al.[16] found that the 5A allele of matrix metalloproteinase-3 was associated with the occurrence of CAE. Also, CAE was 6 times more frequent among patients with familial hypercholesterolemia than in a control group, suggesting a link between abnormal lipoprotein metabolism and aneurysmal CAD.[17] We believe that the increased thrombophilia gene polymorphism detected in symptomatic CAE is a new genetic factor that may contribute to the diagnosis of these patients.

Gene polymorphism may be affected by regional, ethnic, and other variances. In order to make an optimal comparison, the study population should be similar. Some studies conducted in Turkey have observed that an endothelial nitric oxide synthase (eNOS) gene 894G>T polymorphism might be a risk factor for the development of CAE. Ekmekçi et al.[5] demonstrated that the eNOS intron 4a/b gene was a risk for CAE formation. These 2 studies showed that a polymorphism in the eNOS gene could cause CAE formation. In addition, 2 studies have been conducted in Turkey related to the role of the ACE gene. Uyarel et al.[18] reported that the DD genotype of the ACE gene was a risk factor for CAE formation. Similarly, Gülec et al.[15] found the same result. In our study, the incidence of thrombophilia mutations was significantly higher in the CAE group, but we did not find the gene responsible for this result.

A study conducted in China determined that the human 8-oxoguanine DNA glycosylase gene Ser326Cys variant was a risk factor in the development of CAE.[19] Akdemir et al.[20] found that variants in the human leukocyte antigen class II gene could play a role in the formation of CAE. In another study, İçli et al.[21] showed that carrying the A allele of the beta-fibrinogen-455G>A gene polymorphism posed a risk for CAE. They found that the gene polymorphism was present in 68% of the patients with CAE and 30% in the control group. However, in our study, the frequency of beta-fibrinogen-455 G>A gene polymorphism was similar between the CAE and control groups (48% in the control group and 36% in the CAE group). This difference could be due to differences in the number of control subjects or regional genetic variation.

Factor V Leiden (G1691A), factor V H1299R, prothrombin G20210A, factor XIII V34L, PAI-1 4G/5G, MTHFR C677T, and MTHFR A1298C gene polymorphisms have been shown to affect the formation of atherosclerosis.[22–25] Although the pathophysiology and risk factors of CEA are similar to atherosclerosis, our study findings revealed for the first time that the frequency of these 8 thrombophilic gene polymorphisms was significantly higher in CAE. Our research indicated that there may be a link between thrombosis and CAE, as has been observed by many clinicians in daily life. However, these data should be confirmed by further studies with more patients and more detailed genetic investigations.

Study limitations

The effect of gene polymorphism still seems to be inadequate to clearly demonstrate a causal relationship to CAE. The small number of cases is a significant limitation of our study. Also, it was difficult to determine the type of CAE. The lack of other secondary thrombophilic disorders (e.g., high lipoprotein-a level, presence of anti-phospholipid and anti-cardiolipin antibodies, and protein C, S, and antithrombin III deficiencies, etc.) might be another limitation, since the risk of thrombosis increases with the increase of numbers of thrombophilic factors. Finally, the patients we included in the study do not represent all CAE patients because they were symptomatic patients undergoing coronary angiography. This might be a group among CAE patients with a higher risk of thrombosis. It should be confirmed by a more comprehensive study that includes asymptomatic CAE patients.

Conclusion

Our study findings showed that the frequency of thrombophilia gene polymorphisms was significantly higher in CAE patients. However, there was no difference on an individual gene basis for 3 most common gene polymorphisms. It should be keep in mind that regional, ethnic, and genetic variation may have role in gene polymorphism. These results should be clarified in larger studies to determine if patients with CAE have a higher tendency to thrombosis due to hereditary thrombophilia.

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