Association between endothelial nitric oxide synthase intron 4a/b polymorphism and aortic dissection

Endotelin nitrik oksit sentaz intron 4a/b polimorfizmi ve aort diseksiyonu arasındaki ilişki

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ABSTRACT

Objectives: The genetic risk factors that contribute to the risk of developing aortic dissection (AD) have been studied. We assessed the association of endothelial nitric oxide synthase (eNOS) gene polymorphism with AD.

Study design: Patients who underwent surgery with the diagnosis of AD and survived after the operation in our center between May 2007 and June 2011 were recruited retrospectively. The eNOS intron 4a/b polymorphism was determined by polymerase chain reaction (PCR) using oligonucleotide primers (sense: 5'-AGGCCCTATGGTAGTGCCTTT-3'; antisense: 5'-TCTCTTAGTGCTGTGGTCAC-3') that flank the region of the 27 bp VNTR in intron 4.

Results: Thirty-nine patients (88%) had type A AD, while the remainder (12%) had type B AD. The distribution of eNOS4 a/b gene polymorphism differed significantly from the control group, with higher frequencies of eNOS 4a/a and 4a/b genotypes in the AD group (χ^2=7.16, p=0.03).

Conclusion: In this study, the distribution of eNOS genotypes differed between the AD and control groups; however, this polymorphism was not found to be an independent factor for the development of AD.

ÖZET

Amaç: Aort diseksiyonu (AD) gelişimine neden olan genetik risk faktörleri araştırılmıştır. Bu çalışmada endotelin nitrik oksit sentaz (eNOS) gen polimorfizmi ile AD ilişkisini araştırdık.

Çalışma planı: Mayıs 2007 ile Haziran 2011 tarihleri arasında merkezimizde AD tanısı ile ameliyat olan ve sağ kalan hastalar geriye dönük olarak çalışmaya alındı. eNOS intron 4a/b polimorfizmi, 27 bp VNTR intron 4'teki bölgenin yanını dolduran oligonükleotid primerler (sense: 5'AGGCCCTATGGTAGTGCCTTT-3'; antisense, 5'-CTCTTAGTGCTGTGGTCAC-3') kullanılarak polimeraz zincir reaksiyonu (PCR) ile tespit edildi.

Bulgular: Otuz dokuz hastada (%88) tip A diseksiyon, geri kalanda (%12) tip B AD vardı. eNOS 4a/b gen polimorfizmi dağılımına baktığımızda AD grubunda eNOS 4a/a ve eNOS 4a/b sıklığı kontrol grubuna göre anlamlı olarak daha sık idi (χ^2=7.16, p=0.03).

Sonuç: Bu çalışmada, AD ve kontrol grubu arasında eNOS genotip dağılımı farklı bulunmasına rağmen, bu genetik polimorfizmin AD gelişimi için bağımsız bir faktor olduğu gösterilememiştir.

Aortic dissection (AD) is a catastrophic cardiovascular disease (CVD) occurring secondary to formation of a tear in the intimal layer of the aorta that causes blood flow between the true aortic lumen and a false lumen extending through the aortic wall. [1] The most important predisposing factors for acute AD are hypertension (HT), atherosclerosis, vasculitis (such as giant cell arteritis, Takayasu arteritis, rheu-

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matoid arthritis, and syphilitic aortitis), disorders of collagen (e.g., Marfan syndrome, Ehlers-Danlos syndrome, annulo-aortic ectasia), bicuspid aortic valve, and Turner syndrome.[2-4]

Abnormalities of nitric oxide (NO) metabolism may contribute to endothelial dysfunction and atherosclerosis.[5,6] Genetic polymorphisms, including the variable number of tandem repeat (VNTR) polymorphism in intron 4 (eNOS 4a/b polymorphism), have been shown to affect NO metabolism and increase the risk for cardiovascular events.[6-11] Additionally, the eNOS gene polymorphism has been shown to be associated with HT.[12,13]

In AD, formation of intimal tear and dissection represents the end point of chronic atherosclerotic and inflammatory changes in the aortic wall. It is possible that impaired metabolism of NO secondary to genetic predisposition may influence the aortic wall. Our study was therefore aimed to investigate the possible correlation of eNOS gene polymorphism with AD.

PATIENTS AND METHODS

Patients

A total of 44 patients who underwent surgery with the diagnosis of AD and survived after the operation in our center between May 2007 and June 2011 were assessed retrospectively. The diagnosis of AD was based on the demonstration of an intimal flap with a true and false lumen using imaging techniques including echocardiography and computed tomography. The cases were classified according to the DeBakey classification.[14] All of the patients were contacted by telephone, and a detailed personal history was obtained. Physical examination, laboratory assays and genetic analysis were performed. Patients were diagnosed as hypertensive if their blood pressure was ≥140/90 mmHg or if they were receiving any antihypertensive medication. Other risk factors for AD including diabetes mellitus (DM) (defined as fasting glucose level >126 mg/dl on 2 occasions or a previous diagnosis of DM), hypercholesterolemia (a low-density lipoprotein (LDL) level >130 mg/dl or usage of anti-hyperlipidemic medications), and hypertriglyceridemia (defined as a fasting triglyceride level >150 mg/dl or usage of anti-hypertriglyceridemia medications) were also recorded. Patients with iatrogenic, traumatic or syndromic AD were excluded. Eighty age- and gender-matched individuals who had normal findings on their physical and echocardiographic examination were recruited as the control group. The study protocol was approved by the ethics committee of our hospital, and all participants provided written informed consents.

Abbreviations:

AD	*Aortic dissection*
DM	*Diabetes mellitus*
HT	*Hypertension*
MCP-1	*Monocyte chemo attractant protein-1*
PCR	*Polymerase chain reaction*
VNTR	*Variable number of tandem repeat*

Genetic polymorphism analysis

The eNOS intron 4a/b polymorphism was determined by polymerase chain reaction (PCR) using oligonucleotide primers (sense: 5'-AGGCCCTATGGTAGTGCCTTT-3'; antisense: 5'-TCTCTTAGTGCTGTGGTCAC-3') that flank the region of the 27 bp VNTR in intron 4. Reactions were performed in a total volume of 50 µL containing 100 ng genomic DNA, 10 pmol of each primer, 0.2 mM dNTP, 1 U Taq DNA polymerase, and 5 µL PCR buffer (500 mmol/L KCl, 100 mmol 3-hydroxymethyl-aminomethane chloride and 0.8% Nonidet P40). The thermocycling procedure consisted of initial denaturation at 94°C for 1 min, annealing at 58°C for 1 min, and extension at 72°C for 1 min. The PCR products were analyzed using 3% agarose gel electrophoresis 90 V for 1 hour and visualized by ethidium bromide staining. The large allele, eNOS4b, contains 5 tandem 27 bp repeats, and the smaller allele, eNOS4a, contains 4 repeats. The sizes of PCR products were 393 bp and 420 bp for eNOS4a and eNOs4b alleles, respectively.

Statistical analysis

All statistical analyses were performed with the Statistical Package for the Social Sciences version 16 (SPSS Inc., Chicago, IL, USA). Descriptive statistical results are presented in the tables as means±standard deviations. The frequencies of the genotype distribution (4a/a, 4a/b, 4b/b) were compared between patients and controls by chi-square and Fisher's exact tests. The distribution of genotypes within groups was in accordance with the distribution predicted by the Hardy-Weinberg equilibrium model. Continuous variables between patients and controls were compared using the independent sample t-test and Mann-Whitney U-test. Logistic regression analyses were performed to investigate the possible predictors of AD in the study population. All tests were two-sided,

and a p-value <0.05 was considered significant.

RESULTS

The study population consisted of 44 patients with AD (mean age, 56.7±10.8 years) and 80 controls (mean age, 55.7±9.2 years). Baseline characteristics of the study groups are shown in Table 1. The AD group was comparable to controls regarding age, gender and clinical characteristics. However, HT was more prevalent (p<0.001), creatinine levels were higher (p=0.02), and platelet counts were lower (p=0.01) in the AD group compared to the controls. Thirty-nine patients (88%) had type A, and the remaining 5 (12%) had type B AD.

The distribution of eNOS4 a/b polymorphism differed significantly from the control group, with higher frequencies of eNOS a/a and a/b genotypes in the AD group (χ^2=7.16, p=0.03) (Table 2). The frequency of allele "a" of the eNOS 4a/b polymorphism was also significantly higher in the AD group (χ^2=5.45, p=0.02). The distribution of the genotypes in hypertensive subjects (n=63) was not significantly different from that in normotensive subjects (n=61) (p=0.08). The frequencies of the genotypes were as follows: in hypertensive patients a/a: 4.7%, a/b: 22.2%, and b/b: 73.1%, and in normotensive patients a/a: 0%, a/b: 13.1%, and b/b: 86.9%. In addition, genotype distribution was similar between diabetics and non-diabetics (p=0.78) and subjects with or without hyperlipidemia (p=0.96).

In the regression analysis, HT was the only independent predictor of AD in the study (odds ratio [OR]: 4.96, 95% confidence interval [CI]: 2.03-12.12; p<0.01) (Table 3). Presence of the allele "a" was weakly correlated with AD in the univariate regression analysis and was not a predictor of AD in the multivariate regression analysis.

DISCUSSION

According to this study, even though the presence of 'a' allele was more frequent in the AD patients and it was weakly correlated with the presence of AD, regression analysis did not show a significant correlation between AD and the eNOS 4a/b polymorphism. The only independent correlate of AD was HT.

Aortic dissection is among the cardiovascular diseases with the highest morbidity and mortality rates. Although many etiologic factors are defined, such

Table 1. Baseline demographics and biochemical characteristics of the aortic dissection and control groups

	Aortic dissection (n= 44)			Controls (n=80)			*p*
	n	%	Mean±SD	n	%	Mean±SD	
Clinical data							
Age±SD (years)			56.7±10.8			55.7±9.2	0.62
Male/female	34/10			59/21			0.66
Hypertension	33	75		11	13		**0.01**
Current smoker	27	61		26	32		**0.002**
Diabetes mellitus	2	4		6	7		0.52
Hyperlipidemia	2	4		6	7		0.52
Aortic dissection classification							
Type A	39	88					–
Type B	5	12					–
Laboratory findings							
Creatinine(mg/dL)			1.45±1.26			0.98±0.12	**0.02**
Hemoglobin (g/dL)			10.1±1.2			11.3±2.9	**0.08**
WBC (10^3 /μL)			10.8±4.5			8.7±3.6	**0.09**
Platelet (10^3 /μL)			195.5±101.1			272.7±106.1	**0.01**

SD: Standard deviation; WBC: White blood cell count.

Table 2. Allele frequencies and genotype distribution of endothelial nitric oxide synthase (eNOS) 4a/b polymorphism in the aortic dissection and control groups

	Aortic dissection (n=44)		Control (n=80)	
	n	%	n	%
eNOS 4a/b gene polymorphism				
a/a	3	6	0	0
a/b	10	22	12	15
b/b	31	70	68	85
Total n (%)			χ^2=7.16, p=0.028	
Allele frequency*				
a	16	18	12	8
b	72	82	148	92
Total	88	100	160	100
			χ^2=5.45, p=0.02	

*Direct gene counting method was used to calculate allele frequency.

Table 3. Univariate and multivariate regression analysis of possible predictors of aortic dissection in the study population

Variable	OR (95% CI)	*p*	OR (95% CI)	*p*
Age (1-SD increase)	1.01 (0.97-1.05)	0.59	–	
Male	1.83 (0.78-4.24)	0.16	–	
Hypertension	5 (2.2-11.3)	**<0.01**	4.65 (2.1-10.6)	**0.01**
Diabetes mellitus	1.91 (0.45-8.01)	0.38	–	
Smoking	1.67 (0.79-3.53)	0.18	–	
eNOS 4a/b polymorphism				
Presence of a/a genotype*	NA	NA		
Presence of a/b genotype*	1.82 (0.71-4.68)	0.21		
Presence of allele “a”	2.37 (0.97-5.79)	0.06	1.9 (0.72-4.87)	0.19

*b/b genotype of the eNOS 4a/b polymorphism was used as the reference group.

as HT, connective tissue disorders, vasculitis, chest trauma, pregnancy (typically in the third trimester or early postpartum period), and bicuspid aortic valve, genetic risk factors are still unclear and need to be investigated.[1,15,16] Previous studies have shown an association between ACE gene polymorphism and matrix metallopeptidase-1 gene polymorphism and AD.[12,13] To our knowledge, this is the first study investigating the relationship between AD and eNOS 4a/b polymorphism.

In this trial, we found that the distribution of eNOS 4a/b polymorphism was different in subjects with AD and controls. The frequencies of eNOS a/a and a/b genotypes and allele “a” of the eNOS 4a/b polymorphism were higher in patients with AD compared to the control group. However, in the regression analysis, the presence of allele “a” did not reach statistical significance (p=0.06). The study group and control group were comparable except for the prevalence of HT, which is a well-known risk factor for AD. HT was the only independent predictor of AD. Similarly, in the IRAD registry, 71% of the AD patients had a history of HT.[3] A relation between HT and eNOS gene polymorphism was shown previously.[17,18] However, we did not observe a correlation between eNOS 4a/b polymorphism and HT.

Nitric oxide (NO) is derived from L-arginine and molecular oxygen by a family of three enzymes, the eNOS.[19] It contributes to vascular tone regulation and inhibits platelet aggregation, leukocyte adhesion to vascular endothelium and smooth muscle cell migration and proliferation.[20-24] Inhibition of NO synthesis induces inflammatory changes and monocyte chemoattraction, which have been assumed to be early events in vascular disease.[25] It has been shown that NO modulates the expression of the monocyte chemoattractant protein-1 (MCP-1)[26] *in vitro*, and reduced NO synthesis may produce inflammatory and proliferative changes *in vivo*. Thus, endogenous NO synthesis may decrease MCP-1 in endothelial cells and monocytes and may contribute to the anti-atherotic and arteriosclerotic effects of endothelial NO.[27]

These vital actions of eNOS are likely to prevent the development of atherosclerotic plaque. In the IRAD registry data, atherosclerosis was found in the history of 31% of the patients.[3] Polymorphism of the eNOS gene may affect the functional activity of eNOS and its modulating effects on atherogenesis. Previously, Tsukada et al.[5] showed that presence of the allele "a" of the eNOS 4a/b polymorphism may cause lower levels of plasma NO. Similarly, Song et al.[28] reported that this polymorphism may also affect the transcriptional activity of the eNOS gene and enzyme activity.

The clinical and prognostic importance of eNOS 4a/b polymorphism has been shown previously in different clinical conditions. Asanuma et al.[29] demonstrated that the "a" allele of the eNOS 4a/b polymorphism may affect the prognosis of hemodialysis patients with low levels of serum high-density lipoprotein. Basaran et al.[30] observed that the eNOS gene intron 4 VNTR polymorphism is linked with the pathogenesis of vascular access thrombosis. Fatini et al.[31] showed that carotid atherosclerosis was significantly associated with the "a" allele and the combined genotypes of "a" allele with other eNOS gene polymorphisms. Ichihara et al.[8] found that the presence of eNOS 4a allele was an independent risk factor for myocardial infarction, especially in patients having no other traditional risk factors. Furthermore, a relation between eNOS polymorphism and abdominal aortic aneurysm had also been shown.[32] Hence, the negative effects of eNOS 4a allele on atherosclerosis may occur independent of traditional risk factors.

In conclusion, we showed in this trial the association between eNOS 4a/b polymorphism and AD. Although we could not demonstrate the independent role of this polymorphism in AD risk, our findings may contribute to the data regarding the complex interactions between endothelial dysfunction, inflammation and vascular deterioration predisposing to AD.

Limitations

The main limitations of our study are its retrospective design, the relatively small sample size and enrollment of only living patients. However, considering the low prevalence of the disease and high mortality rates, it is difficult to conduct a prospective trial about the genetic susceptibility to AD. Another limitation is that markers of oxidative stress and inflammation and other eNOS gene polymorphisms associated with atherosclerotic and vascular phenotypes in population studies, such as -786T→ C and Glu298→Asp, were not studied. Prospective studies with larger groups of patients and including different polymorphisms of the eNOS gene are needed to determine the pathogenetic link between eNOS gene polymorphism and AD.

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Key words: Aortic dissection; eNOS enzyme; genetic predisposition to disease; genotype; introns/genetics; nitric oxide; polymorphism, genetic.

Anahtar sözcükler: Aort diseksiyonu; eNOS enzimi; genetik predispozisyon; genotip; intronlar/genetik; nitrik oksit; polimorfizm, genetik.