The relationship between angiotensin converting enzyme gene polimorphism and lacunar infarction

Laküner infarkt ve anjiotensin dönüştürücü enzim gen polimorfizmi arasındaki ilişki

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Abstract

Background: To evaluate the relationship between polymorphisms of the angiotensin converting enzyme (ACE) gene and cerebral lacunar infarction.

Methods: We included 23 patients with cerebral lacunar infarct confirmed with computerized tomography (CT), and 26 controls with normal CT scans. We considered age, sex, hypertension, diabetes mellitus, cardiac disease, hyperlipidemia and smoking as risk factors. Insertions or deletions (I/D) in the ACE gene were detected using polymerase chain reaction (PCR).

Results: The average incidence of hyperlipidemia and mean age were higher in the lacunar infarct group ($p<0.01$ and $p<0.05$, respectively) than in the control group. There was no difference in the frequencies of I/D polymorphisms in the ACE gene between groups .

Conclusion: We did not find an association between I/D polymorphisms in the ACE gene and lacunar infarction.

Key words: Lacunar infarction, ACE gene polymorphism, genetic

Özet

Amaç: Serebral laküner infarktlar ile anjiyotensin dönüştürücü enzim (ADE) gen polimorfizmi arası ilişkiyi araştırmak.

Materyal ve metot: Çalışmaya bilgisayarlı tomografisinde laküner infarkt tespit edilen 23 hasta ile bilgisayarlı tomografisi normal olan 26 kontrol dahil edildi. Risk faktörleri olarak yaş, cinsiyet, hipertansiyon, diyabet, kalp hastalığı, hiperlipidemi ve sigara içimi alındı. Polimerize zincir reaksiyonu kullanılarak ADE geninde insersiyon delesyonlar araştırıldı.

Bulgular: Laküner infarkt grubunda ortalama hiperlipidemi insidansı ve ortalama yaş kontrol grubundan daha yüksek bulundu ($p<0.01$ ve $p<0.05$). Her iki grupta ADE geninde I/D polimorfizminde sıklık açısından fark tespit edilmedi.

Sonuç: Laküner infarktlar ile ADE geni I/D polimorfizmi arasında bir ilişki bulamadık.

Anahtar kelimeler: Laküner infarkt, ADE polimorfizm, genetik

Introduction

Stroke is the third most common cause of death in the world. Stroke pathogenesis is multifactorial. The genetic predisposition to stroke is unclear in most cases, but genetic factors may modify or predispose to developing risk factors, such as hypertension (1). Genetic effects are mostly polygenic and different ischemic stroke phenotypes have different genetic profiles (2).

Previous studies have investigated candidate genes in

the pathogenesis of stroke. These studies have mostly examined genes that may be associated with risk factors of stroke.

Genes that influence the renin-angiotension system are potentially of etiologic importance for cardiovascular diseases (3). In 1990, an insertion/deletion (I/D) polymorphism within the angiotensin converting enzyme (ACE) gene was discovered, which is responsible for the variance of serum ACE concentrations in the normal population (4). The I/D polymorhism in intron 16 of the ACE gene has been extensively studied in cardiovascular diseases. It has been shown that subjecs having DD genotype have twice the ace concentration in plasma than do subjects with the II genotype (5). However, the results of studies that have examined the role of this polymorphism in ischemic stroke are inconsistent. Some studies have shown an association between the ACE gene DD genotype and lacunar stroke (1). This seems plausible as the gene encoding ACE is thought to be an important candidate for cerebral small vessel disease due to the enzyme's role of in hypertension, endothelial function, and the regulation of smooth muscle proliferation and tone (6).

If the hypothesis of the role of the ACE gene in small vessel disease is true, this knowledge should be very usefull for both in treatment and preventive strategies. Therefore, in the present study, our aim was to investigate whether the ACE gene I/D polymorphism is a risk factor for small cerebral vessel disease.

Material and method

Twenty-three patients were admitted to the Ondokuz Mayıs University Neurology Clinic with acute stroke and lacunae on brain CT (group 1), and twenty-six healthy controls (group 2) were enrolled in the study. Controls were selected from individuals, who had no history of cerebrovascular disease and normal CT findings. All the participants were white.

Detailed information was collected on the medical history and risk factors for stroke including hypertension, hyperlipidemia, diabetes mellitus, coronary heart disease and smoking .

Before taking blood samples, informed consents were obtained from all patients.

Venous blood samples were collected in tubes with EDTA from subjects to extract genomic DNA. PCR was performed by using primers that flank the I/D region in intron 16 of the ACE gene, as described by Rigat et al. with some modification (7).

Statistical analyses were conducted with SPSS (Statistical Package for Social Sciences for Windows version 11.0 Chicago, IL, USA) software. Differences in age were tested with the student's t test, while other risk factors were tested with the Chi-squared test. The Chi-squared test and Fisher's exact test, were used to investigate the differences in the means of the phenotypic characteristics among the three ACE genotypes. A p value of less than 0.05 was considered statistically significant.

Results

Forty nine subjects were enrolled in the study. The case group included 10 women and 13 men;the control group included 16 women and 10 men. Demographic data of are summarized in table 1. The mean age in the case group was 69.1 ± 7.7 years, and it was 60.6 ± 7.1 years in the control group. Hypertension was found in 18 patients (78%), and in 16 control subjects (61,5%)($p>0.05$). Diabetes mellitus was observed in five patients (21.7%), and in nine control subjects (34.6%) ($p>0.05$). Among stroke patients, 30.4% had coronary hearth disease, 39.1% had hyperlipidemia and 21.7% were smokers. Among control subjects, coronary hearth disease was present in 15.9%, hyperlipidemia was present 11.5%, and there were no smokers.

Genetıc analysis

The ACE II genotype was found in seven patients

(30%), and two controls (7.7%), while the ACE ID genotype was found in six patients (26.1%) and 13 controls (50%). Among cases, there were ten subjects with the the ACE DD genotype, and among controls, there were ten subjects (table 2 and figure 2). We compared the frequency of the ACE DD genotypes and the ACE II+ID genotypes in cases and controls, using the Fisher's test (figure 1). There was no istatistically significant difference between in the ACE gene polymorphisms between the two groups ($p>0.05$).

Discussion

In our study, we did not observe differences in the frequency of the ACE I/D genotypes between the patient and control groups. The aim of this study was to evaluate the association between ace gene polymorphisms lacunar stroke.

There are many studies that have shown an association between the ACE gene polymorphism and stroke, although there are also many studies that have not found a correlation. It has been reported that risk factors, such as hypertension, were seen at nearly the same frequencies in the case and control groups. On the other hand, cardiac pathologies responsible for emboli and carotid stenosis were seen less frequently in patients with lacunar infarcts. These findings point to the possibility that lacunar infarcts must be studied as an isolated entity (8). Kario et al. found a positive association between the ACE DD allele and ischemic stroke in japanesen hypertensives (3). Those authors concluded that this association was independent of other risk factors, including left ventricular hypertrophy as detected by electrocardiogram. Thus, the ACE DD allele may be an independent risk factor for the development of cerebrovascular disease in hypertensive patients.

A study from South India showed that the ACE ID/DD genotypes were associated with an elevated incedence of stroke in large vessel disease, which conflicts with results that showed an association in small vessel disease (1, 9). Similarly, Saidi et al. found an associatian for the ACE gene DD genotype and large vessel disease in a Tunisian population (10). An investigation in China also showed that the ACE DD allele was a risk factor for large artery arteriosclerosis (11). Kostulas et al. reported an association between an ACE gene polymorphism and both carotid artery stenosis and ischemic stroke (12).

Hassan et al. studied 87 patients with lacunae to determine whether there was an associatian between the ACE gene polymorphism and leukoaraiosis (6). They found that the ACE DD genotype was seen more frequently in patients with leukoaraiosis; however, there was no control group in this study. Markus et al. found that the deletion polymorphism in the angiotension-converting enzyme gene was a new independent risk factor for lacunar stroke but it was not a risk factor for stroke associated with carotid stenosis (1). However, Pullicino noted that recurrent strokes make it difficult to be able to determine the association between the DD genotype and a particular subtype of stroke (13). According to another study, the frequency of the DD genotype of the ACE gene was significantly higher in subjects with cerebral infarction than in those without cerebral infarction (14).

In a metaanalysis of the ACE gene and ischemic stroke concluded that the D allele, acting recessively, is a modest but independent risk factor for ischemic stroke (15).

Snolzki et al. detected the ACE DD genotype more frequently in the patients with small-vessel pathologies than in the control subjects. However, in that study, no imaging was carried out for the controls, so the clinically stroke-free controls could still have had silent brain infarcts; this could

have biased the genotype differences between the subgroups and the control group (16).

In a study from Poland, different stroke subgroups were enrolled in a study. In this study, 96 subjects had small vessel disease, but they found no association between the ACE I/D polymorphism and different stroke subtypes (17). Pullicino et al. also found no association between AGE gene polymorphisms and different stroke subtypes, but no control group was included in their study (13).

There are a few studies about this subject in a Turkish population . Celiker et al. examined 162 patients who had different stroke subtypes. They found that the DD genotype was more frequent in all stroke groups (18). In contrast, Tuncer et al. found no association between ACE I/D genotypes in 168 ischemic stroke cases and normal control subjects (19).

Our study has some limitations. First of all, we have a small sample size, and we did not compare lacunar group with other stroke subtypes. In recent studies, some investigators found that the ACE DD polymorphism was a risk factor in large artery disease so we believe that large studies including all stroke subtypes are needed to fully investigate this question.

We tried to match the control and patient groups as closely as possible, but in the patient group, age and serum cholesterol levels were higher than the control group. However, if we would have found gene polymorphism frequencies that were higher in the patient group, those imbalances might have been a greater limitation for interpreting the results.

Studies evaluating ACE gene polymorphism and stroke showed that this polymorphism was not a major risk factor but there is still a need to investigate this polymorhism in small vessel diseases and large vessel disease in different racial populations. In conclusion, this study showed no association between the ACE I/D polymorphism and lacunar infarct in this small study group.

Table 1: Risk analysis of the groups

	Patient group		Control group		X^2 value	*P* value
	N	%	n	%		
Mean age	69.1 ± 7.7		60.6 ± 7.1		t=4.2	<0.01
Female	10	43.5	16	61.5	1.59	>0.05
Male	13	56.5	10	38.5		
Hypertension	18	78.3	16	61.5	1.6	>0.05
Diabetes Mellitus	5	21.7	9	34.6	0.99	>0.05
Cardiac disease	7	30.4	4	15.9	1.58	>0.05
Hypercholesterolemia	9	39.1	3	11.5	5.02	<0.05
Smoking	5	21.7	0	0		

Table 2: Genotype analysis of the groups

	Patient group		Control group		X^2 value	*P* value
	N	%	N	%		
ACE DD Genotype	10	43.5	11	42.3	5.24	>0.05
ACE II Genotype	7	30.4	2	7.7		
ACE ID Genotype	6	26.1	13	50		
TOTAL	23	100	26	100		

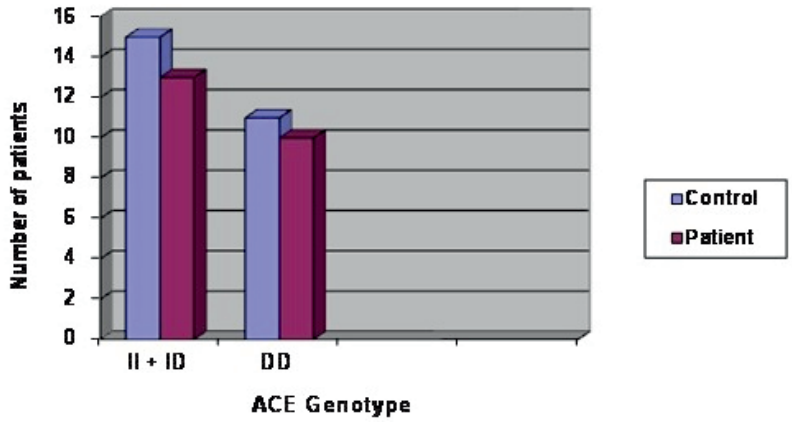

Figure 1: Genotype analysis of DD and II+ID groups

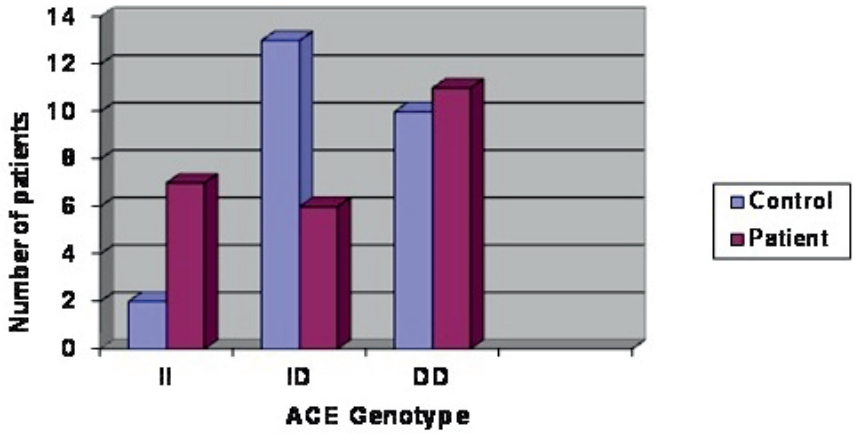

Figure 2: Genotype analysis of the groups

Yazarlarla ilgili bildirilmesi gereken konular (Conflict of interest statement) : Yok (None)

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