vidual variation is rare (4). It is also reported that serum ACE levels tend to be higher in blacks in comparison to whites (5). Cambien et al., reported familial resemblance of ACE levels in a large family study (6). These observations suggest the probability of genetic or racial differences in serum ACE levels in patients with sarcoidosis.

After cloning of human endothelial ACE gene, a genetic control of plasma ACE levels has been suggested by the identification of an I/D polymorphism of the ACE gene (7). In 1996 Furuya et al., reported a significant association between ACE gene polymorphism and serum ACE levels and suggest to investigate ACE gene polymorphism as a marker for increased risk of sarcoidosis (8).

This study is designed to investigate the probable association between the ACE gene I/D polymorphism and risk of sarcoidosis and tuberculosis.

Methods

Subjects

Forty eight consecutive patients with sarcoidosis (31 female and 17 male), aged 18-67 years (mean age 40 years) were included in the study. The diagnosis of patients with sarcoidosis was based on the combination of characteristic clinical features together with histopathological evidence of non-caseating granuloma in biopsies.

Fifty one consecutive patients with tuberculosis (17 female, 34 male), aged 16-60 years (mean age 28 years) were included in the study. The diagnosis of tuberculosis was made either by a positive smear or culture of sputum or bronchial lavage, or the presence of caseating granuloma in a biopsy sample.

In our previous study, hundred and six healthy subjects (55 female and 51 male and mean ages 26 and 31 years respectively), all of Turkish descent and with no history of parental consanguinity were enrolled in the study with informed consent (9). All the subjects responded a questionnaire including their medical history, parental origin and consanguinity. Thus, a study population with parental origin from all the regions of Turkey. That study represents Turkish population genetically, before we used the results of that study as a control group in the present study.

Detection of ACE gene polymorphism

For genotyping experiments, 10 mL venous blood was obtained in a sterile vacutainer containing EDTA. Each individual in the study was informed about his/her ACE genotype with a DNA analysis report.

Genomic DNA extracted from peripheral blood leukocytes by the modified method described elsewhere (10). We amplified the insertion/deletion portion in intron 16 of the ACE gene by polymerase chain reaction (PCR) method of Rigat et al. (11). In homozygous DD samples a second PCR reaction with primers that recognize an insertion spesific sequance was performed. The amplification products of the first PCR were electrophoresed in 3% agarose gels and those of the second reaction in 1.5% agarose gels and visualized by ethidium bromide staining under UV light (Figure 1). The PCR results were scored by two independant investigators and no interobserver variability was found. All ambigious samples were analysed a second time.

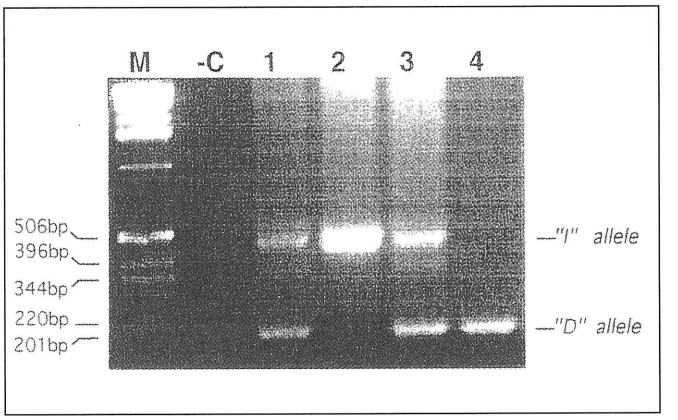

Figure 1. *PCR amplification products of I/D portion of intron 16 of ACE gene*

Statistical analysis

The frequency of allele and genotypes were compared by using the chi-square test with an Instat-2 programme. The p value <0.05 was considered to be significant.

Results

Table 1 shows the distribution of genotype frequencies in patients with sarcoidosis, tuberculosis and healthy subjects. In healthy subjects, the frequency of the D allele was 59%

Table 1. Allele and genotype frequencies of ACE gene insertion/deletion polymorphism in sarcoidosis, tuberculosis and healty Turkish population

	ALLELE		GENOTYPE		
GROUP	D (%)	I (%)	DD (%)	DI (%)	II (%)
Sarcoidosis (n=48)	58.3	41.7	33.3	50.0	16.7
Tuberculosis (n=51)	47.1	42.9	23.5	47.1	29.4
Control (n=106)	59.0	41.0	35.9	46.2	17.9

p= 0.5522 (chi-square test)

and the I allele 41%. The genotype distribution was 35.9% for DD, 46.2% for DI and 17.9% for II. Although there are slight differences, the allele and genotype frequency values for healty Turkish population are in agreement with the previously published Caucasian population frequencies. There was also no frequency difference between patients with sarcoidosis and patients with tuberculosis.

It has been reported that ID heterozygous individuals for the ACE gene may be misgenotyped as DD homozygous due to preferential amplification of the D allele. Therefore, a second PCR reaction aiming at only the intron-specific sequences was recommended (12). 10 patients in sarcoidosis group, 5 patients in tuberculosis group and twelve patients in the control group were later identified as ID in the second PCR whether they identified as DD according to the first PCR.

Discussion

Serum ACE activity is an important marker for disease activity in patients with sarcoidosis. High serum activity is also reported to be an unfavorable prognostic factor.
However, the prevalence of increased serum ACE levels ranged from 33% to 88%, thus it has low sensitivity and spesificity.

After cloning of ACE gene, a genetic control of serum ACE levels has been suggested by the identification of an I/D polymorphism of the ACE gene. In 1996, Furuya et al., reported a significant association between ACE gene polymorphism and serum ACE levels both in patients with sarcoidosis and in controls. In their study they found that reference interval for SACE levels depends on the distribution of the three ACE genotypes in a given population (8). And they recomended to discriminate abnormal serum ACE levels more accurately by determining the three reference intervals for each genotype. Later on in 1997, Sharma et al., confirmed the suggestions of Furuya et al. Shama et al., reported that 33.3% improvement in assessing serum ACE levels by concomitant determination of ACE genotype and serum ACE levels (13).

It appears that the presence or absence of allele D is associated with higher or lower serum ACE levels in patients with sarcoidosis (8). If the whole reference interval is used, serum ACE level is underestimated in patients with genotype II and overestimated in patients with genotype DD (8,13).

Since ACE gene allele and genotype frequencies differs in various populations, every population should determine their individual frequency of ACE gene I/D polymorphism and normal values of serum ACE for each genotype (8,14,15).

In the present study, we determined the frequency of allele and genotype of ACE gene in patients with sarcoidosis and tuberculosis and compared the results with healthy controls. The frequency of ACE gene polymorphism in patients with sarcoidosis was not different from that in healthy controls. Serum ACE levels can increase also in other granulamatous diseases so we compared the results of sarcoidosis patients with the results of tuberculosis patients and did not find any difference (16). Table 2 shows the comparison of allele and genotype frequencies between Turkish and Japanese patients and controls. It is obviously seen that the frequency of D and I alleles are equal in Turkish population but I allele is more frequent in Japanese population. Similarly DD genotype is not the less frequent genotype in Turkish population as it is in Japanese population. This study was aimed to investigate whether ACE gene polymorphism is a risk factor for the development of sarcoidosis or other ACE related diseases such as tuberculosis. However, the present data do not allow us to conclude that the ACE gene I/D polymorphism is an increased risk factor for sarcoidosis or tuberculosis. Indeed, genotype frequency differences encountered in two populations but sarcoidosis is seen in both countries. On the other hand, both tuberculosis and sarcoidosis are granulamotous diseases and there was not ACE gene genotype frequency difference, serum ACE levels increases are relatively more common and higher in sarcoidosis (16).

Tablo 2. ACE genotype and allele frequencies in the present study and in the study of Furuya et al.

	Present Study		Furuya et al.	
	Sarcoidosis (N=48)	Control (N=106)	Sarcoidosis (N=103)	Control (N=341)
DD (%)	33.3	35.9	14	14
ID (%)	50.0	46.2	51	40
II (%)	16.7	17.9	35	46
D (%)	58.3	59.0	39	33
I (%)	41.7	41.0	61	67
P value	NS		NS	

In conclusion, since concomitant determination of ACE gene genotypes and serum ACE levels are necessary for the accuracy of serum ACE assessing in individual countries or populations, initiation of a national collaborative study on ACE gene polymorphism should be planned by the members of the Turkish Thoracic Society

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Thoracic Manifestations of Behçet's Disease: Reports of the Turkish Authors

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Abstract

Background: Behçet's disease (BD) is a multi systemic disease, not only confined to the Mediterranean, Middle Eastern and Asian countries as believed previously, but may also be found worldwide. Turkey is one of the countries where BD is common.

Setting: In this study, thoracic manifestations of BD were reviewed by collecting and reevaluating the case reports and case series reported by the Turkish authors. The parameters were selected as the age, gender, duration of the disease, pulmonary and extrapulmonary symptoms/findings, laboratory findings, types of the pulmonary/vascular manifestations, radiological findings, treatments and outcomes.

Results: Between 1958 and 1998, 63 cases were reported. Additionally, there were well defined case series of pulmonary manifestations of BD consisting of a total of 156 cases. Male gender and young age were the dominant demographics (among the case reports, 94% was male and the mean age was 30 years). Hemoptysis was the most common symptom in BD with thoracic involvement (64%). 54% of vascular involvement was found as pulmonary artery aneurysm.

Conclusion: Only a well-informed physician can identify BD and features of thoracic involvement. Because of the poor prognosis, massive hemoptysis in a patient with characteristics of mucosal ulceration should alert the physician to consider the development of the pulmonary artery aneurysm.

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Key words: *Behçet's Disease, thoracic involvement, massive hemoptysis, pulmonary artery aneurysm*

Introduction

Behçet's disease (BD), a syndrome of an unknown etiology described by the Turkish dermatologist Hulusi Behçet in 1937, is a multi systemic disease. It is not only confined to the Mediterranean, Middle Eastern and Asian countries as believed previously, but it is also found worldwide (1). The cardinal manifestations of this syndrome are aphthous stomatitis, genital ulceration, and ocular involvement. The involvement of the dermatological, venous or arterial, arthritic, central nervous system and gastrointestinal system are the other possible manifestations. Pulmonary

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