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Characterization of Angiotensin Converting Enzyme Gene Polymorphism and Risk of Different Heart Diseases

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Abstract

Background: The present work aims to test the association of angiotensin converting enzyme (ACE) gene insertion/ deletion (I/D) polymorphism in patients with myocardial infarction (MI).

Subjects and Methods: The study comprised 79 Egyptian cases with MI. Their mean age was 54.4± 9.9 years including 60 (75.9%) males and 19 (24.1%) females, 23 (29.1%) were smokers, 21 (26.6%) had a positive family history of MI, 25 cases (31.6%) were diabetic, 16 cases (20.3%) were hyperlipidemic. For comparison, 238 healthy subjects of nearly matched age and sex ., with no history of any cardiac diseases were taken as a control group. For all subjects , DNA testing for ACE gene I/D polymorphism was done using PCR amplification to detect both D and I alleles followed by a second run PCR specific for the I allele for cases typed as DD in the first run.

Results: Cases had higher frequency of DD (29.1%) and ID (62%) than II (8.9%) genotype with a higher frequency of D allele than I allele (64.4% vs 33.6%). Compared to controls, cases had significantly higher frequency of ID genotype (62% versus 47.5%, $P<0.05$). Cases with low risk factors had a higher frequency of ID genotype compared to controls (66.7% vs. 47.5%, $P=0.002$). The same was, also, found in the high risk group but with a lower level of significance (63.6% vs 47.5%, $P=0.041$).

Conclusion: ACE gene polymorphism is probably a risk factor for ischemic heart disease among Egyptian cases particularly if integrated with other environmental and genetic risk factors.

Key words: ACE polymorphism, Egypt, Myocardial infarction

Introduction

Coronary artery disease (CAD) is multifactorial disease and influenced by environmental and genetic factors. Family history of premature CAD in addition to other risk factors such as smoking, obesity, diabetes, and dyslipidaemia would give better clues as to the likelihood of the occurrence of the disease ***(Egred et al.,2005).*** Although the role of these environmental factors in the development of MI has been clearly established, the role of non-conventional risk factors remains undefined. In the last few years a great interest has been focused on genetic factors with the intent to find common markers that could identify a subgroup of patients at higher risk of death or with a worse prognosis in which new therapeutic timings and interventions could be tested ***(Franco et al.,2007).***

In the enzymatic cascade, angiotensinogen (AGT) is cleaved by renin to produce angiotensin I, which is further converted in the bioactive octapeptide angiotensin II (ATII) through the action of angiotensin I converting enzyme (ACE), a membrane-bound, zinc metalloendopeptidase involved in the metabolism of many small peptides. ACE and AGT are important in blood pressure and blood volume homeostasis ***(Petrovic et al.,2001).*** Thus, it is not surprising that the genes coding for that system are being investigated in relation to myocardial infarction ***(Franco et al.,2007).***

Concentrations of plasma and tissue ACE are determined by the ACE gene located at chromosome 17q 23. That gene manifests a 287 bp of a repeated Alu

sequence insertion (I) or deletion (D) polymorphism in intron 16 ***(Ranjith et al.,2004).*** The homozygous DD genotype, which is associated with a two- to three-fold increase in levels of ACE, may cause a variety of adverse cardiovascular effects ***(Danser et al.,1995).*** The increased risk of MI associated with the ACE D allele is graded, with low risk for ACE II, intermediate risk for ACE ID, and high risk for ACE DD genotypes which suggest codominant inheritance ***(Cambien et al.,1992, Steeds et al.,2001).*** It is hypothesized that in subjects with the ACE DD genotype, higher levels of ACE may contribute to coronary thrombogenesis ***(Ohira et al.,2004).***

The aim of the current study is to investigate the possible association of ACE gene polymorphism with myocardial infarction among cases from the Nile Delta region of Egypt.

Subjects and Methods

The present study comprised 79 cases with myocardial infarction taken randomly from those admitted in the Intensive Care Units (ICU) of Cardiology Department, Internal Medicine Specialized Hospital, Mansoura University, Egypt. Their mean age was 54.4±9.9 years with an age range of 25-75 years. They were in the form of 60 (75.9%) males and 19 (24.1%) females. Of them, 23 (29.1%) were smokers, 21 (26.6%) had a positive family history of myocardial infarction, 25 cases (31.6%) were diabetic, 16 cases (20.3%) were hyperlipidemic. Regarding risk factors, cases were classified into high risk group with 2 or more risk factors and low risk group with no or only one risk factor. For comparison, 238 healthy subjects of nearly matched age and sex and with no history of any cardiac diseases were taken as a control group. Informed consent was taken from all subjects in addition to an approval from the University Ethical and Scientific Committees.

Determination of ACE I/D polymorphism

For all subjects, DNA was extracted from peripheral blood samples followed by PCR amplification of the respective fragments from intron 16 of the ACE gene according to the method described by Lindpaintner *et al.*(1995). Briefly, 20 ul of a PCR master mix containing 1mM primers, 200 mM deoxynucleoside tripho-sphates, 1.3 mM magnesium chloride, 50 mM potassium chloride, 10 mM TRIS–hydrochloric acid (pH 8.4 at 25°C), 0.1 percent Triton X-100, and 0.35 unit of Taq polymerase was added. Optimized primer pair was used to amplify the D and I alleles, resulting in 319-bp and 597-bp amplicons, respectively (5'_GCCCTGCAGGTGTC-TGCAGCATGT3'_; and 5'_GGATGGC-TCTCCCCGCCTTGTCTC3'_). The therm-ocycling profile (Techne, Genius, UK) consisted of denaturation at 94°C for 30 seconds, annealing at 56°C for 45 seconds, and extension at 72°C for 2 minutes, repeated for 35 cycles, followed by a final extension at 72°C for 7 minutes. The amplification products of the D and I alleles were identified by electrophoresis on 2% agarose gel and visualized on 300-nm ultraviolet transilluminator. Because the D allele in heterozygous samples is preferentially amplified, each sample found to have the DD genotype was subjected to a second, independent PCR amplification with a primer pair that recognizes an insertion-specific sequence (5'_TGGGA CCACAGCGCCCGCCACTAC3'_;and 5'_TCGCCAGCCCTCCCATGCCCATAA 3'_), with identical PCR conditions except for an annealing temperature of 67°C. The reaction yields a 335-bp amplicon only in the presence of an I allele, and no product in samples homozygous for DD. (Fig.1).

Statistical analyses

Data were processed and analyzed using the Statistical Package of Social Science (SPSS, version 10.0). The frequency of studied allelic polymorphisms among cases was compared to that of controls and tested for positive association using chi-square ($\chi 2$), Fisher's exact tests and odds ratio (OR) with 95% confidence interval (95%CI). A minimum level of significance is considered if P is ≤ 0.05. Furthermore, the distribution of alleles in studied groups was tested for fitting to the Hardy-Weinberg equilibrium assuring no significant difference between observed and expected frequencies using $\chi 2$ test.

Results

The distribution of ACE gene polymorphism in studied cases of MI and controls (table 1) showed that cases had higher frequency of DD and ID than II genotype (29.1%, 62% and 8.9% respectively). Compared to controls, cases had significant lower frequency of DD genotype (29.1% vs. 47.5% , P<0.05) but with significant higher frequency of ID genotype (62% vs. 47.5%, P<0.05). On the other hand, cases showed higher frequency of II genotype than controls which is statistically non-significant (8.9% vs. 5%, P>0.05). Meanwhile, total cases showed higher frequency of D allele than I allele (64.4% vs. 33.6%) but with significant lower frequency when compared to controls, (64.36% vs. 71.22%, P<0.05 for D allele and 33.64% vs. 28.78%, P<0.05 for the I allele).

Comparison of ACE genotypes among low risk and high risk subjects with controls using $\chi 2$ test of trend (table 2) showed that low risk cases had higher frequency of ID (66.7%) than controls (47.5%) which is statistically significant (P=0.002). The same was observed in the high risk group but with a lower level of significance (63.6% vs 47.5%, P=0.041).

On the other hand, comparing ACE genotype frequencies in cases-subgroups related to each single risk factor as age of onset, sex, hyperlipedemia, smoking, positive family history, diabetes and obesity revealed no significant difference.

Table 1. Shows Distribution of ACE gene polymorphism in a sample of acute myocardial infarction compared to controls.

From this table, It is noticed that cases had significant lower frequency of DD genotype than controls (29.1% versus 47.5%, P<0.05). Also, it is noticed that cases had significant higher frequency of ID genotype than controls (62% versus 47.5%, P<0.05). On the other hand, cases showed higher frequency of II genotype than controls which is statistically non-significant (8.9% versus 5%, P>0.05). Meanwhile, total cases showed significant lower frequency of D allele (64.36% versus 71.22%, P<0.05) and significant higher frequency of I allele than controls (33.64% versus 28.78%,P<0.05). Finally, in both groups of Egyptian cases and controls, we observed that the frequency of D allele is higher than the frequency of I allele.

Table 2. Shows Distribution of ACE genotype among low risk and high risk subjects compared to controls using $\chi 2$ test of trend. From this table, it is noticed that ID genotype had the highest frequency (66.7%) followed by DD (20%) and II (13.3%) genotype in Low risk cases which is statistically significant (P=0.002). Also, ID genotype had the highest frequency (63.6%) followed by DD (29.5%) and II (6.8%) genotype in High risk cases which is also statistically significant (P=0.041).

Number 1 was marker which used; Numbers 2,3,4,5,6,7,8 were myocardial infarction cases.

- Panel A (PCR products, first run) with P1, P2 show positive bands for both D allele (319bp) and I allele (597bp).
- In the figure there are two bands for both D allele and I allele in lanes 3,5,7,8. i.e: ID genotype in lanes 3,5,7,8 and only one band for the D allele in lanes 2, 4, 6.i.e: DD genotype in lanes 2, 4, 6.
- Each sample found to have the DD genotype was subjected to a second independent PCR amplification with P_3, P_4.
- Panel B (PCR products, second run) with P3, P4 show positive band for the I allele (335bp) in lanes 2,3, 5, 7 and 8. This denotes that these cases are actually a ID genotype.

Table 1. Distribution of ACE gene polymorphism in a sample of acute myocardial infarction compared to controls

	Cases (n=79)	Controls (n=238)	Fisher P	OR (95% CI)
Genotypes				
DD	23 (29.1%)	113 (47.5%)	0.0057**	0.45(0.26-0.79)
ID	49 (62%)	113 (47.5%)	0.027*	1.81(1.07-3.04)
II	7 (8.9%)	12 (5%)	0.27	1.80(0.69-4.83)
Alleles	(n=158)	(n=476)		
D	95(64.36%)	339(71.2%)	0.01*	0.61(0.42-0.88)
I	63(33.64%)	137(28.78%)	0.01*	1.64(1.13-2.39)

OR (95% CI) : odds ratio (95% confidence intervals)
** P <0.01 * P <0.05 (Significance level testing each group vs. controls)

Table 2. Distribution of ACE genotype among low risk and high risk subjects compared to controls using χ^2 test of trend

Studied groups	ACE Genotypes			χ^2	P
	DD n (%)	ID n (%)	II n (%)		
Controls (n=238)	113(47.5)	113(47.5)	12(5.0)		
Total Cases (n=79)	23(29.1)	49 (62.0)	7 (8.9)	8.28	0.004**
Low risk Cases (n=30)	6 (20)	20 (66.7)	4 (13.3)	9.58	0.002**
High risk Cases (n=44)	13 (29.5)	28 (63.6)	3 (6.8)	4.18	0.041*

five cases dropped from the analysis with non-informative history to be assigned to particular risk group
** P <0.01 * P <0.05 (Significance level testing each group vs. controls)

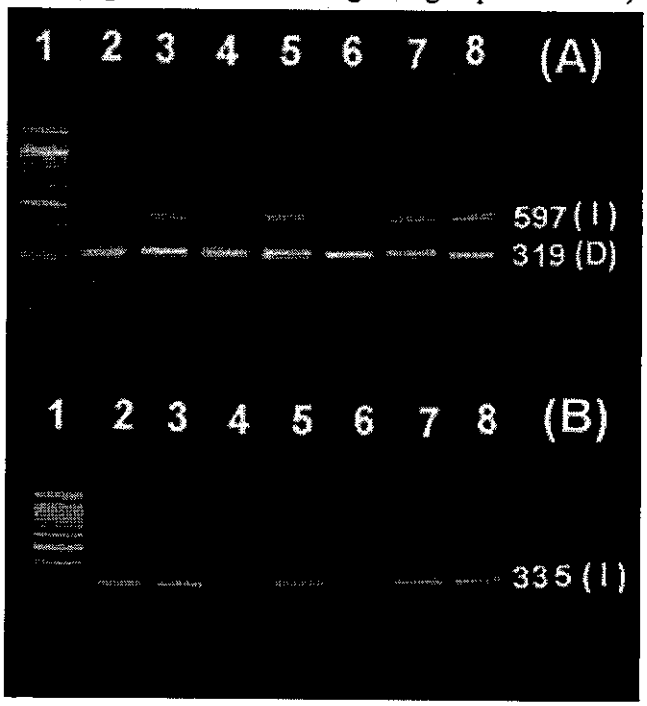

Figure 1. Shows Amplification of ACE gene in myocardial infarction cases.

Discussion

Coronary heart disease (CHD) continues to be the main cause of death in developed countries. During the last decade there has been a growing interest in the study of ACE gene insertion/deletion polymorphism as a potential risk factor for different heart diseases like myocardial infarction ***(Chambless et al.,1997).*** However, despite the large number of studies with different designs and populations, the role of ACE gene polymorphisms on MI is still controversial ***(Igic and Behnia.,2003).***

The current study of ACE polymorphisms among Egyptian controls showed an equal frequency of ID and DD genotypes that is relatively high (47.4% each) with lower frequency of II genotype. The same finding was, also, reported by Nduna et al.(1999) in Saudi Arabia (47.1% for DD and 41.0% for ID) and Aucella et al. (2000) in Italy (44.5% and 42.8% respectively). However, several other studies showed higher frequency of ID among their control groups (ID genotype frequency is one and half to two times as much as the DD). Examples include Mizuiri et al.(1995) in Japan, Sagnella et al.(1999) in South Asia, Jalil *et al.(*1999) in Chile , Huang *et al.* (1998) in Australia, Marre et al.(1997) in France, Lindpaintner *et al.* (1995) in USA and Schmidt *et al.* (1995) in Germany.

Regarding ACE polymorphism among Egyptian MI cases, the present study showed higher frequency of ID than DD genotypes with lower frequency of II genotype. The frequency of D allele was, also, higher than the frequency of I allele. This is in agreement with most studies like Bautista *et al.*(2004) in Colombia, Agrawal *et al.*(2004) in India, Nduna et al.(1999) in Saudi Arabia, Hamon et al.(2003) in France, Zak et al.(2003) in Poland and Franco *et al.*(2007) in Italy. However, compared to controls, the current study showed higher significant frequency of the ID genotype among MI cases but with significant lower frequency of the DD genotype. The same finding was reported by Nduna et al.(1999) in Saudi Arabia. Also, in Turkey, Acarturk et al.(2005) reported that the ID genotype was the most frequent in all subjects underwent diagnostic coronary angiography although in cases found to have CAD, the DD genotype was higher compared to the controls. In Poland, Zak et al.(2003) reported that the D allele carriers (DD + ID genotypes) were more frequent in the CAD patients compared to control group, whereas the familial CAD risk group showed the highest frequency of the ID genotype.

The lower frequency of DD genotype observed among cases may be due to the fact that their sample was restricted to fresh MI cases of the present study rather than the ambulant cases under maintenance treatment. Here, it could be speculated that the cases with DD genotype can manifest early with alarming signs of hypertension or mild angina and receive treatment as ambulatory cases. On the other hand, cases with ID, that are speculated to have an intermediate elevation of ACE enzyme, can be neglected until coming under effect of other risk factors that lead together to the outcome of acute MI. This is manifested by having 63% of the present cases with 2 or more risk factors. In that respect, a bigger sample including both acute cases with MI in addition to ambulatory cases with ischemic heart disease considering at the same time the various risk factors pertaining to the disease is recommended.

Studies stressing the possible role of ACE DD genotype as a risk factor in CAD related to disease prognosis in terms of disease onset and mortality includes Cambien et al.(1992) in France, Palmer et al. (2003) in New Zealand, Keavney et al. (2000) in UK, Bautista et al. (2004) In Colombia, Alvarez et al. (2001) and Mata-Balaguer *et al.* (2004) in spain and Ranjith *et al.* (2004) in young South African Indians.

However, in Rotterdam Study (Netherlands), Sayed-Tabatabaei et al. (2005) observed an increased risk of cardiovascular mortality for carriers of the D allele of the ACE I/D polymorphism among smokers. That difference was only observed in younger people and diminished

at later ages. No association was observed between the ACE I/D polymorphism and MI. Agrawal et al.(2004) in India and Franco et al.(2007) in Italy observed that the DD genotype was slightly higher in patients as compared to controls; however, the differences were not significant.

It could be concluded that ACE gene polymorphism is probably a risk factor for ischemic heart disease among Egyptian cases particularly if integrated with other environmental and genetic risk factors.

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تمييز الطرز الجينية للإنزيم المحول للأنجيوتنسين ومخاطر الإصابة بأمراض القلب المختلفة

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موت جزء من عضلة القلب (الاحتشاء القلبي) الحاد يعرف بالأزمة القلبية وهو مرض ينتج عن انقطاع إمداد الدم عن القلب مما يسبب تلف وموت جزء من العضلة القلبية وهو من الأمراض الرئيسية المسببة للوفيات فى جميع أنحاء العالم. وتعد طفرة جين الأنجيوتنسين واحدة من أخطر العيوب الو راثية في العالم والتي تسبب ميل الدم إلى التجلط مما يسبب انسداد أحد الشرايين الممدة بالدم لعضلة القلب مما يتسبب في انقطاع الدم عن جزء من العضلة القلبية مما يؤدى إلى موته.لذا كان الهدف من هذا البحث هو تحديد الطرز الجينية للإنزيم المحول للأنجيوتنسين بين المصريين المصابين بمرض الاحتشاء القلبي بالمقارنة بمجموعة من الأصحاء.

أشتمل هذا البحث على79 حالة تعاني من الاحتشاء القلبي اختيرت بشكل عشوائي من مرضي العناية المركزة بوحدة القلب بمستشفى الباطنة التخصصي ، جامعة المنصورة ، مصر. وقد كان متوسط أعمارهم 54.4 ± 9.8 عام وتم تقسيمهم تبعا للجنس إلى 60 ذكر و 19 أنثى. وقد تضمن البحث أيضا 238 من الأصحاء لا يعانون من أي مرض خاصة الأمراض القلبية كمجموعة ضابطة وذلك لتحليل خطر ظهور طفرة جين الأنجيوتنسين مقارنة بالمجموعة الضابطة.

وقد خضعت كل الحالات المرضية والحالات الضابطة لتحديد الطرز الجينية للإنزيم المحول للأنجيوتنسين ولهذا الغرض تم جمع عينات من الدم الوريدي للحالات في أنابيب بولى إثيلين تحتوى على محلول EDTA للحصول علي محتواها من DNA ثم تم استخلاص وتنقية محتواها من DNA عن طريق تقنية Purification Capture Column (System USA Gentra) للحصول علي عينات DNA جاهزة للتحليل .

تعيين طفرة جين الأنجيوتنسين:

يتم تكثير الجين المسئول عن هذه الطفرة باستخدام البادئات المناسبة (Primers) عن طريق تفاعل البلمرة المتسلسل (PCR).

النتائج التي حصلنا عليها كانت كما يلي:

1– قد كانت نسبة ظهور المجموعة ذات الطراز الجينى المختلط (ID) عالية بين الحالات المرضية (62٪) مقارنة بالمجموعة الضابطة (47.5٪) (P< 0.05, O.R = 1.18) and (95% CI = 1.07-3.04)

2- وقد كانت نسبة ظهور المجموعة ذات الطراز الجينى المتشابه (DD) أقل بين الحالات المرضية (29.1٪) مقارنة إلى المجموعة الضابطة (47.5٪)-0.26 = (95% CI and (P< 0.05, O.R = 0.45) 0.79)

3- وبالتالى كانت نسبة ظهور الطراز الجينى D (64.36٪) أعلى من نسبة ظهور الطراز الجينى I (33.64٪) عند المصريين المصابين بالاحتشاء القلبي .

وقد أتضح من نتائج هذه الدراسة أن:

أن طفرة جين الأنجيوتنسين موجودة عند بعض المصريين المصابين بالاحتشاء القلبي .

النسبة العالية للطراز الجينى (ID) لجين الأنجيوتنسين تشير إلى العلاقة العالية بين هذه الطفرة الجينية والاحتشاء القلبي بين الحالات المصرية.

نسبة ظهور الطراز الجيني (D) أعلي من نسبة ظهور الطراز الجيني (I) عند المصريين المصابين بالاحتشاء القلبي .