



## Insertion/deletion polymorphism of the angiotensin I-converting enzyme gene in migraine patients

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### Abstract

Several authors reported an association between the Angiotensin Converting Enzyme (ACE)-D allele and coronary artery disease. The mechanism on the basis of this association is unclear.

Recently, it has been suggested that the ACE-DD polymorphism may play an important role in the determinism and in the frequency of migraine attacks. Therefore, the aim of our study was to determine the incidence of ACE polymorphism in a consecutive series of migrainous patients (ICHDII-2004 diagnostic criteria) and of patients affected by myocardial infarction.

We studied a series of 51 migrainous patients aged 38.6 years +/- 18.8 (8 MWA and 43 MWA, ICHDII-2004 criteria) come at our observation in the period 2005-2006. The control group was composed by 58 patients affected by Acute Myocardial Infarction (AMI) admitted to the ICCU (Intensive Coronary Care Unit) of S.Luca Hospital in Vallo della Lucania in the same period. Exclusion criteria from the study were: positive anamnesis for analgesic abuse, presence of serious diseases, need to take drugs for other pathologies. The analyse was based on Polymerase Chain Reaction (PCR) and on reverse-hybridization and included 3 steps: 1 DNA isolation from non coagulated blood, 2 PCR amplification using biotinylated primers, 3 hybridization of amplification products to a test strip containing allele-specific oligonucleotide probes immobilized as an array of parallel lines. Bound biotinylated sequences were detected using streptavidin-alkaline phosphatase and an appropriate color substrate.

16 (42%) migrainous patients and 32 (56%) cardiopathy patients had an ID genotype; 19 (50%) migraineurs and 20 (34%) cardiopaths had a DD genotype.

The results of our study confirm the association between migraine and ACE I/D genetic polymorphism. These data are confirmed in the sample of patients affected by myocardial infarction.

This gives evidence of a strong relationship between migraine and major vascular diseases and let us hypothesize an important role of ACE system in the pathogenetic model of migraine for its capability to interfere with the endothelial regulation tone.

Once an effective role in the genesis of migraine and in the increased risk of migrainous patients to evolve into an ischemic pathology has been obviously assigned to this genetic mutation, future researches must aim through wider and more controlled casistics also to clarify the role that drugs acting on these systems may have on the resolution of these diseases.

KEY WORDS: ANGIOTENSIN CONVERTING ENZYME, GENE POLYMORPHISMS, MIGRAINE

## Introduction

Migraine is a neuro-vascular syndrome characterized by recurrent headache attacks associated with photophobia, phonophobia, nausea and vomiting. Migraine occurs in about 18 % of women and 6% of men, regardless of race or geographical location [1]. Currently, migraines are divided into two categories: migraine without aura (previously termed common migraine), and migraine with aura (previously also termed classical migraine) preceded by a 15-20 minute episode of visual or sensory aura. Auras are most commonly visual alterations, such as hemianopsic field defects and scotomas that enlarge and spread peripherally [2] Visual auras are associated with spreading cortical depression; sensory auras are usually experienced as paraesthesias of the arm and face.

While the exact etiology of migraine headaches is unknown, several theories have been proposed. The vascular theory attributes migraines to an initial intra-cranial arterial vasoconstriction, resulting in reduced blood flow to the visual cortex, followed by a period of extra-cranial vasodilation [3]. Modern imaging techniques have shown that during a common migraine attack there are in fact only minor changes in cerebral blood flow, and the proposed initial vasoconstrictive phase may actually last much longer than the aura [4]. It has also been hypothesized that migraine sufferers have an inherent vasomotor instability and are more susceptible to the vasodilatory effects of certain physical and chemical agents. This point of view has been reinforced by the observation that organic nitrates, which are capable of delivering nitric oxide, trigger migraine attacks in migraineurs, at low doses, ineffective in normal subjects [5].

Moskowitz's theory involves the trigeminovascular complex, which links the aura and the headache of migraine [6]. In this theory the trigeminovascular neurons release substance P and other neurotransmitters in response to various triggers.

Several authors reported an association between the Angiotensin Converting Enzyme (ACE)-D allele and coronary artery disease. The mechanism on the

basis of this association is unclear.

Recently [7] it has been suggested that the ACE-DD polymorphism may play an important role in the determinism and in the frequency of migraine attacks. These data have been confirmed by Kowa et al [8] according to which the D allele and the DD genotype in ACE gene is a risk factor for Japanese for migraine without aura. Contrasting results have been noticed, indeed, by Linn et al [9] who have highlighted a slight protective effect against migraine for ACE-DD polymorphism in male patients. On the base of these data it's possible to suppose there's a relationship between ACE activity and migraine.

The aim of our study was to determine the incidence of ACE polymorphism in a consecutive series of migrainous patients (ICHDII-2004 diagnostic criteria) and of patients affected by myocardial infarction.

## Methods

We studied a series of 51 migrainous patients aged 38.6 years +/- 18.8 (8 MWA and 43 MWA, ICHDII-2004 criteria) come at our observation in the period 2005-2006. The control group was composed by 58 patients affected by Acute Myocardial Infarction (AMI) admitted to the ICCU (Intensive Coronary Care Unit) of S.Luca Hospital in Vallo della Lucania in the same period. Exclusion criteria from the study were: positive anamnesis for analgesic abuse, presence of serious diseases, need to take drugs for other pathologies. The analyse was based on Polymerase Chain Reaction (PCR) and on reverse-hybridization and included 3 steps: 1 DNA isolation from non coagulated blood, 2 PCR amplification using biotinylated primers, 3 hybridization of amplification products to a test strip containing allele-specific oligonucleotide probes immobilized as an array of parallel lines. Bound biotinylated sequences were detected using streptavidin-alkaline phosphatase and an appropriate color substrate.

## Results and Conclusions

16 (42%) migrainous patients and 32 (56%) cardiopathy patients had an ID genotype; 19 (50%) migraineurs and 20 (34%) cardiopaths had a DD genotype (Fig 1 and 2).

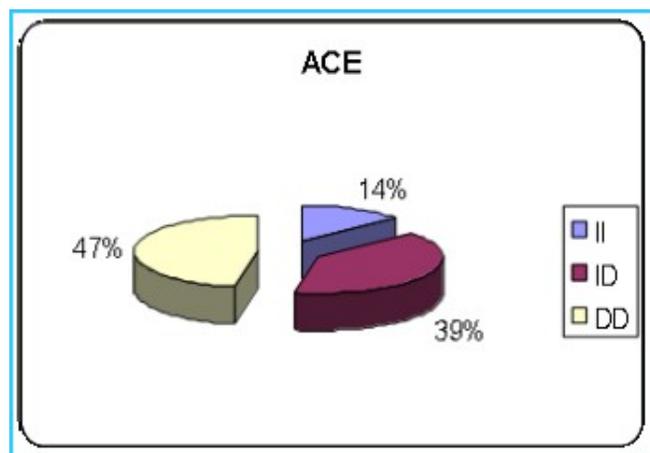


Fig. 1. ACE polimorfism in the migrainous group

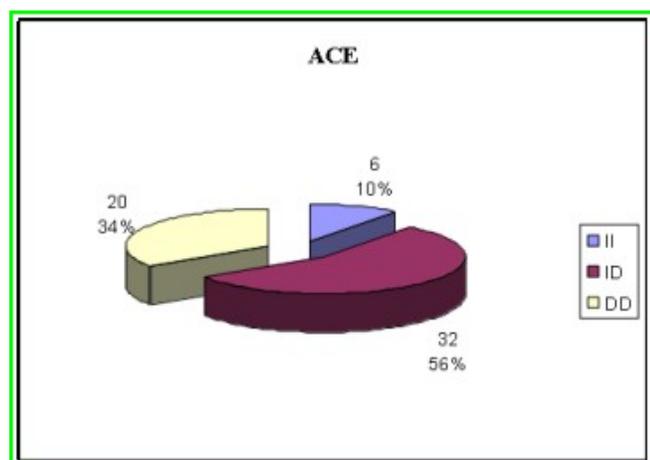


Fig. 2. ACE polimorfism in the cardiopathy group

The results of our study confirm the association between migraine and ACE I/D genetic polymorphism. These data are confirmed in the sample of patients affected by myocardial infarction.

Genetic aspects underlying common forms of migraine are not clear, but the wide clinical spectrum of migraine suggests that several polymorphisms may interact to determine its manifestation and gravity, while the effect of a single mutation is thought to be minimal.

Recently, several angiotensin I-converting en-

zyme (ACE) inhibitors and an angiotensin II receptor blocker were demonstrated to have a clinically important prophylactic effect in migraine. ACE is one of the key enzymes in the rennin-angiotensin-aldosterone system, which modulates vascular tension and blood pressure [7]. In humans, serum ACE levels are strongly genetically determined. Individuals who were homozygous for the deletion (D) allele showed increased ACE activity levels. To investigate the role of ACE polymorphism in headache, we analyzed the ACE insertion (I)/deletion (D) genotypes of 54 patients suffering from migraine with aura (MwA), 122 from migraine without aura, 78 from tension-type headache (TH), and 248 non-headache healthy controls [7]. The ACE D allele were significantly more frequent in the MwA than controls. The incidence of the D/D genotype in MwA (25.9%) was significantly higher than that in controls (12.5%). No differences in the remaining groups were found. These findings indicate that the D allele and the D/D genotype in the ACE gene is a genetic risk factor for MwA thus suggesting a possible relationship between ACE activity and the pathogenesis of migraine [7].

Paterna et al. [8] evaluate if the DD genotype could also be associated with the frequency and duration of migraine without aura. In 302 patients suffering from migraine without aura, the genotypes of the ACE gene, plasma ACE activity, and the frequency (weekly) and duration of migraine attacks were evaluated. No drugs were given before (4 weeks) and during the study. The same evaluations were performed in 201 subjects without migraine. Patients with migraine without aura showed higher incidence of the ACE-DD gene (48.34%) than control subjects (37.32%). The frequency of migraine (average attacks per week) was higher in patients with DD (2.11 +/- 1.9) than in patients with ID (1.54 +/- 1.44). No difference in duration of migraine attacks (hours per week) was observed. Plasma ACE activity was increased in patients with the ACE-DD gene. These data suggest that ACE-DD gene polymorphism could have an important role in determining migraine attacks and the frequency of these attacks [8].

Also, angiotensin converting enzyme (ACE) gene has been implicated as a genetic factor associated with migraine [9]. A case-control study was performed to investigate the association between ACE and migraine in 240 migraine patients and 200 healthy controls [9]. There was no significant difference in allelic frequency (I and D) and genotype polymorphism (DD, DI and II) of the ACE gene in migraine patients and controls. Analysis of the difference in ACE polymorphism stratified by gender revealed that male migraine patients with the homozygote DD genotype (ACE-DD) were significantly fewer than that of male controls. There was no existence of a difference among the frequency and duration of headache in each subgroup of migraine patients stratified by ACE genotype. These findings indicate that ACE-DD may have a slight protective effect against migraine in male patients [9].

This gives evidence of a strong relationship between migraine and major vascular diseases and let us hypothesize an important role of ACE system in the pathogenetic model of migraine for its capability to interfere with the endothelial regulation tone.

Once an effective role in the genesis of migraine and in the increased risk of migrainous patients to evolve into an ischemic pathology has been obviously assigned to this genetic mutation, future researches must aim through wider and more controlled casistics also to clarify the role that drugs acting on these systems may have on the resolution of these diseases.

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