Original Paper • CME

Angiotensin-Converting Enzyme I/D Polymorphism in Patients With Malignant Hypertension

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*The angiotensin-converting enzyme (ACE) gene has been implicated in the manifestation of the phenotype of malignant hypertension (MH). In 1990 the ACE gene polymorphism characterized by the insertion or deletion of a 287-base pair fragment in the 17q23 chromosome was identified. The DD genotype is associated with increased tissue and circulating ACE levels and elevated angiotensin II. ACE polymorphism was studied in 48 patients with MH, 25 patients with non-MH, and a control group of 78 normotensive individuals by real-time polymerase chain reaction using the LightCycler system (Roche Diagnostics Corporation, Indianapolis, IN). The DD genotype was found statistically more frequently in MH patients than controls (*p=*0.028; odds ratio, 2.5; confidence interval, 1.1–5.5). Presence of the DD genotype of the ACE gene is more frequent in MH patients than in controls, indicating that this genotype could be a significant risk factor and a predictor for the development of MH. (J Clin Hypertens. 2005;7:11–17)* ©*2005 Le Jacq Ltd.*

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Epidemiologic and family studies indicate that nearly 30% of individual variation in blood pressure (BP) is determined genetically, and it is now accepted that essential hypertension is a complex, polygenic condition determined by several genes interacting with environmental factors.[1] This would partly explain the great variation in terms of target organ involvement in individuals with comparable BPs.[2]

The renin-angiotensin system plays an essential role in BP control. Angiotensin-converting enzyme (ACE), a key component of the renin-angiotensin system, is a zinc metallopeptidase that inactivates the vasodilator bradykinin and hydrolyzes angiotensin I (AI) to generate the potent vasoconstrictor angiotensin II (AII), which provokes sustained increases in BP by binding to vascular AT1 receptors of angiotensin II. ACE is present on the surface of epithelial and endothelial cells and is also found in circulating form.[3]

In 1990, an ACE polymorphism was identified, characterized by the insertion (I) or deletion (D) of a 287 base-pair fragment in intron 16 of the 17q23 chromosome. The physiological importance of this resides in the fact that the DD genotype has been associated with increased circulating and tissue concentrations of ACE.[4] This has led to the idea that DD patients could have higher AII levels, which would result in increased BP and a greater cardiovascular risk due to elevated AII levels in cardiac and vascular tissues.

Since its description, the I/D polymorphism has been associated with an increased risk for the development and progression of cardiovascular and renal disease.[2,5–7] Some studies have found

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no relation between essential hypertension and the ACE I/D polymorphism.[8] However, two large, prospective studies in different ethnic populations (Japanese Suita and American Framingham) have demonstrated a positive association between the DD genotype and essential hypertension in men, but not in women.[9–10]

Malignant hypertension (MH) is a severe form of hypertension with important target organ involvement, affecting 1%–2% of hypertensive patients.[11] Despite widespread use of antihypertensive medication, this rate had failed to decline in some populations in a study reported 10 years ago.[12] Recent clinical experience, however, suggests that MH is rare, as a result of early treatment of less severe cases. MH is characterized by endothelial damage and myointimal cell proliferation, resulting in pathological changes in the vasculature, including "onion skinning" with endothelial swelling and fibrinoid necrosis.[13] Clinical signs of transformation to the malignant phase include rising BP, renal failure and the development of grade III or grade IV retinopathy.[14]

Absolute BP levels do not completely explain the conversion of benign to MH, since even moderate BP rises (e.g., 150/100 mm Hg) with an acute onset can lead to MH, as in cases of preeclampsia,[15] whereas some patients with very high BP never develop the malignant phase. These facts make us wonder why some patients with essential or secondary hypertension have a particular risk of developing MH, and what pathogenic mechanisms might be responsible for transforming benign to MH.

Experimental models of MH have demonstrated that onset of the malignant phase could depend upon vasoconstricting humoral factors, such as AII, vasopressin, and norepinephrine, which exert additional effects to those produced by BP elevation that can lead to the initiation of MH.[15–16] In the clinical setting, MH has been demonstrated to be an angiotensin-dependent form of hypertension with high renin and angiotensin levels and a high aldosterone secretion rate.[15]

The clinical observation of an increased incidence of MH in certain ethnic groups supports a role for genetic modifiers in determining susceptibility to this condition.[17] It is conceivable that one or more genetic polymorphisms in the individual may interact in response to hypertension and dictate the degree of vascular injury. Being able to predict which patients may be at risk of developing MH and which individuals may not, despite significantly elevated BP, may be a useful clinical finding.

In a previous study, Stefansson et al.[18] showed that the DD genotype of the ACE gene occurred more frequently in MH than in healthy controls. Although the proportion of the DD genotype in the control group of this study did not correspond to previously published percentages,[2,19,20] this series suggested that ACE gene polymorphism could be a significant risk factor for the initiation of MH. Shortly afterwards, Mayer et al.[21] showed an association of the D allele of angiotensin I converting enzyme polymorphism in a variety of pathological entities with histological lesions of malignant vascular injury.

MH represents the most severe form of hypertensive target organ injury, and early identification of persons genetically prone to develop this condition is of particular importance. The present study is directed toward confirming the existence of an association between ACE gene I/D polymorphism and the development of MH. To this end we studied the incidence of this polymorphism in a group of MH patients with severe arterial hypertension and retinal injury, as well as significant involvement of other target organs, including the heart, brain, and kidneys.

SUBJECTS AND METHODS

We retrospectively studied 48 patients diagnosed with MH in our service over the last 27 years (1975–2002). At the time MH was diagnosed, all patients had elevated BP (>165/100 mm Hg) associated with retinal hemorrhage and cottony exudates with or without papilledema. Patients with unilateral involvement or papilledema alone were excluded. Patients with diabetes mellitus were also excluded. Among this group of patients, samples for ACE gene polymorphism studies could be collected. The 48 patients, all Caucasian, were classified as essential or secondary hypertension according to physical examination, urinary protein levels, hormone determinations, and arteriography and/or renal biopsy when considered indicated (n=9; 18.8%). Patients were considered to have renal insufficiency when their serum creatinine concentrations were >1.5 mg/dL and creatinine clearance was <60 mL/min on three separate analyses performed 6 months after the acute phase of MH.

We monitored this group of MH patients in the hypertension outpatient clinic of our hospital, informing them at subsequent visits about the study to be conducted. Both the patients and the subjects in the control group gave informed consent for the gene polymorphism determinations. The study was approved by our hospital's Clinical Research Ethics Committee. Although the clinical diagnosis of MH had been made at different times between 1975 and 2002, the ACE gene polymorphism samples were

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collected during 2002. The group of MH patients included 40 men (83.3%) and 8 women (16.7%), with a mean age of 44.3±12.53 years. Mean systolic pressure was 230.2 mm Hg (±22.07) and mean diastolic pressure was 142.50 mm Hg (±16.44).

In the group of 48 MH patients, grade IV retinopathy was documented in 30 patients (62.5%) and grade III in 18 (37.5%). Twenty-one patients (43.75%) were classified as essential and 12 as secondary (25%) MH; in 15 (31.25%) the etiological process could not be precisely categorized. In the 48 patients with MH, we obtained the following data on target organ involvement: 48 patients (100%) presented severe retinopathy, 30 (62.5%) had left ventricular hypertrophy, 34 (70.8%) had various degrees of renal failure, 7 (14.5%) had brain involvement attributed to hypertension, and 3 (6.25%) had ischemic heart disease. Twenty of the 48 patients with MH (41.6%) had a combination of severe retinopathy, severe renal failure, and severe left ventricular hypertrophy.

The control group was comprised of 78 healthy, Caucasian, unrelated, normotensive individuals, 42 men and 36 women, with a mean age of 36.5±10.6 years, proceeding from the blood donor population of our hospital. We formed another comparison group of patients with non-MH comprised of 25 Caucasians, 13 men, and 12 women, with a mean age of 38.2±9.5 years and with elevated BP (>140/95 mm Hg) and no retinopathy. Extraction of genomic DNA and ACE I/D polymorphism genotyping was carried out using standard techniques.[22]

Statistical Analysis

The chi-square test was used to study associations among categorical variables. The 95% confidence intervals (CIs) for the odds ratio (OR) were calculated according to Cornfield's method. Stratified analysis was used to adjust for possible confounding factors. Epi Info 2000 software (Dean AG and Arner TG, Atlanta, GA) was used for the statistical analyses.

RESULTS

Among the MH patient group, the DD genotype was detected in 25 (52%) patients, ID in 19 (39.5%), and II in 4 (8.3%). Among the 78 control subjects, the DD genotype was observed in 24 (30.8%), ID in 45 (57%) and II in 9 (11.5%). In the group of patients with non-MH, the DD genotype was observed in 9 (36%), ID in 11 (44%) and II in 5 (20%). The DD genotype was statistically more frequent in the MH patients than in the controls (p=0.028; OR, 2.5; CI, 1.1–5.5). We found no statistical differences in the frequency of the DD genotype between patients with non-MH and the control group (p=0.809; OR, 1.27; CI, 0.44–3.59) (Table I). We also found no statistical differences in the frequency of DD genotype between patients with MH and non-MH (p=0.289; OR, 1.93; CI, 0.64–5.89). There was no association between sex and ACE polymorphism in either the patients or the controls.

DISCUSSION

The severe target organ involvement that occurs in MH can lead to blindness, renal failure, or recurring life-threatening episodes of heart failure. These data and the fact that some hypertensive patients with similar BP recordings never develop MH led us to analyze whether or not patients with hypertension and the DD genotype, and therefore higher levels of angiotensin II in tissues, might be more susceptible to developing malignant MH. In the MH group in our study, 20 (41.6%) of 48 patients showed a high incidence of severe target organ involvement presenting a combination of severe retinopathy, renal failure, and left ventricular hypertrophy.

The frequency of the ACE gene DD genotype was statistically higher in MH patients than in the healthy control group. No significant difference in DD genotype distribution was found between the non-MH patients and controls. Finally, although there were evident differences in the percentages of DD distributions between patients with non-MH and those with MH (Table I), the differences were not statistically significant. This last finding may be because of the small size of the non-MH group. What is evident is that the frequency of genotype DD was clearly and significantly higher than in the controls, despite the number of patients evaluated in each group.

Table. Frequency Distribution of ACE I/D Genotypes in Patients With Malignant Hypertension (MH) Compared to Patients With Nonmalignant Hypertension (Non-MH) and Control Subjects

Group	n	DD (n [%])	ID (n [%])	II (n [%])
MH	48	25 (52)*	19 (39.5)	4 (8.3)
Non-MH	25	9 (36)	11 (44)	5 (20)
Controls	78	24 (30.8)	45 (57)	9 (11.5)

Statistical calculation based on the comparison of DD vs. II + DI genotypes. ACE=angiotensin-converting enzyme; I/D=insertion/deletion; *p=0.028; odds ratio, 2.5; confidence interval, 1.1–5.5 compared with control subjects

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To our knowledge, there are very few published studies on ACE I/D polymorphism in MH.[18] Our results are in agreement with those of Stefansson et al., who found a positive association between the DD genotype and the development of MH. However, the normal control subjects in Stefansson's study had DD genotype frequencies considerably lower than in previously reported European studies: 17.6% compared with 30% and 39%.[2,19,20] In contrast, DD frequency in our own healthy control population of 33% was close to that of a large meta-analysis including 135 studies and 19,065 subjects with a quoted frequency of 28%.[21,23,24] This percentage is higher than that reported by Stefansson[18] and provides a more solid basis for the relationship between ACE I/D polymorphism and MH. With regard to the study done by Mayer et al.,[21] these authors also demonstrated the association of the D allele of angiotensin I converting enzyme polymorphism with malignant vascular injury in a heterogeneous group of conditions including MH, scleroderma and hemolytic uremic syndrome. In order establish a definite association between MH and the DD genotype, we believe it is better to have homogeneous groups of patients with MH.[21]

There are strong arguments against elevated BP as the only explanation for the initiation of MH, particularly since it has been observed to occur over a wide range of pressures. It has been suggested that there may be a triggering factor superimposed on benign hypertension that could create a situation of positive feedback which would lead to progressive elevation of BP and further elaboration of the precipitating factor.

Many articles in the literature point to the strong relationship between angiotensin II and the genesis of MH. Acute BP elevation due to noradrenaline, AII infusion, or renal artery clipping can cause the histological changes of MH characterized by endothelial damage and myointimal cell proliferation resulting in pathological changes in the vasculature, including "onion skinning" with endothelial swelling and fibrinoid necrosis.[13]

Other observations suggest that renin or AII is implicated in the transition from the benign to the malignant phase of hypertension. Higher levels of renin and AII have been described in MH patients,[15–16] and a recent study has suggested that the ACE gene could be associated with the development of malignant vascular injury in a transgenic rat model of MH carrying the mouse Ren2 renin gene (TGR[mREN2])27.[25] It is noteworthy that another study has demonstrated that pharmacologic ACE inhibition at sub-hypotensive doses prevents the development of MH in susceptible TGR(mREN2) 27 animals, regardless of whether there is a change in BP.[26]

The ACE gene is highly expressed in endothelial cells and in the heart.[4] In the kidney, ACE mRNA has been demonstrated in endothelial, mesangial, and epithelial cells.[27] Individuals with the DD genotype might have greater local ACE activity and AII levels, which could lead to an increase in intraglomerular pressure and glomerular filtration. This would also stimulate several proto-oncogenes and growth factors, inducing cell hypertrophy, proliferation, and increased cell matrix protein. In this regard, several studies have positively related the D allele or the DD genotype of the ACE gene with the development of target organ injury in essential hypertension. The D allele of the ACE gene has been associated with microalbuminuria, retinopathy, and left ventricular hypertrophy,[6] and the DD genotype has been associated with white-matter brain lesions and nephroangiosclerosis.[2,5,7,28] Moreover, AII inhibition in experimental and human kidney disease reduces histological evidence of kidney damage and slows the progression of chronic renal failure.[29]

The results of the present study demonstrate that the DD genotype is significantly more frequent in patients with MH, which might implicate the I/D polymorphism of the ACE gene as a risk factor for the development of MH and thus be directly related with the considerable target organ injury observed in this entity. These results, together with the other data described, might suggest that patients with arterial hypertension and DD genotype might benefit from early treatment with drugs that inhibit the production or action of angiotensin II. Further study of the genes implicated in hypertension, particularly those of the renin-angiotensin system, are needed in large series of patients with MH, given the phenotypic homogeneity of this group and the severity of the hypertensive disease in these patients.

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CME Questions

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INSTRUCTIONS FOR COMPLETING THIS FORM: Read the selected paper and answer all the questions that follow. After each question there is a series of possibly correct answers. Please select the one best answer for each and place your selection on the answer grid. **YOU MUST ALSO COMPLETE THE CME EVALUATION SECTION** and return the form within 6 months of the paper's publication to receive credit. Letters of credit will be mailed to participants biannually.

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OBJECTIVE AND TARGET AUDIENCE: All primary care physicians and cardiologists are eligible to receive credit. At the conclusion of this activity, participants should be able to: 1) summarize the important points discussed in the paper reviewed; 2) identify patients to whom the paper is relevant; 3) modify management practices as new information is learned; and 4) identify deficiencies in their knowledge base.

Please Select the One Best Answer for Each Question and Place Your Selection on the Answer Grid.

1. Which of the following statements is true?
   - A __ The neuro-endocrine axis has no influence on blood pressure (BP)
   - B __ The inactivation of bradykinin by angiotensin-converting enzyme (ACE) results in vasodilation
   - C __ ACE is localized to the surface of the epithelial and endothelial cells
   - D __ ACE gene polymorphisms may have important effects on BP and the development of cardiovascular and renal disease

2. Which genotype is associated with the highest levels of ACE?
   - A __ DD
   - B __ II
   - C __ ID
   - D __ None of the above

3. Which of the following statements regarding malignant hypertension (MH) is false?
   - A __ Clinical signs of transformation to MH include rising BP, renal failure, and retinopathy
   - B __ In all patients, the development of MH correlates with absolute BP
   - C __ MH is characterized by intimal proliferation and endothelial damage
   - D __ MH is likely angiotensin-dependent

4. Which of the following statements regarding the findings of this study is true?
   - A __ The DD genotype was statistically more frequent in the MH group than in the normotensive group
   - B __ The DD genotype was statistically more frequent in males
   - C __ The DD genotype was statistically more common in all hypertensives compared to the normotensives
   - D __ All of the above are true

5. Which of the following statements regarding the conclusions of this study is false?
   - A __ There is a high incidence of end-organ damage in patients with MH
   - B __ The frequency of the DD genotype is significantly higher in patients with MH than in patients without hypertension
   - C __ There was no significant difference in the incidence of the DD genotype between the patients with MH and the matched group of patients with hypertension without MH
   - D __ All of the above are true

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Questions: 1.__ 2.__ 3.__ 4.__ 5.__

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