ACE I/D Gene Polymorphism in Children with Family History of Premature Coronary Disease

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Letter to the Editor regarding the article by de Albuquerque et al: Angiotensin-converting enzyme genetic polymorphism: its impact on cardiac remodeling.

I read with interest the recent review article by de Albuquerque et al1 published in the Arquivos Brasileiros de Cardiologia entitled “Angiotensin-converting enzyme genetic polymorphism: its impact on cardiac remodeling.” They showed that the DD genotype of Angiotensin-converting enzyme (ACE) gene polymorphism was independently associated with worse echocardiographic outcome, while the DI genotype, with the best echocardiographic profile1.

Atherosclerosis, the major cause of CAD, manifests clinically in adulthood. However, this disease begins very early in life, often during childhood. Genetic and environmental factors, gene–environment interaction effects also come into play in the development of atherosclerosis. Family history is the most significant independent risk factor for CAD.

In our study, we included a total of 140 children, 72 males and 68 females between the ages of 4.9 and 15.7 years. Among these children, 73 had a parental history of premature CAD (parents have been diagnosed with the CAD by coronary angiographic study, ages below 55 for men and 65 for women) and the rest of 67 belonged to our control group (parents have shown normal coronary angiographic study). The participants were screened for the mutations ACE I/D gene polymorphisms.

The genotypes of ACE I/D were significantly different between the study and control groups (p = 0.01). The frequency of D/D genotype was significantly higher in the study group than the control group (respectively, 20/73 vs. 3/67, p = 0.01) (Table 1). The frequency of the D allele was slightly higher in study group (0.52) than in control group (0.27) (p = 0.005).

The angiotensin converting enzyme is a key factor in the production of angiotensin II and in the degradation of bradykinin. Chronic exposure to high levels of circulating ACE concentrations may be associated with an increased risk for development of atherosclerosis. It may be contribute to the detection of the risk of children with a parental history of CAD. Thus, further large population studies must be done to confirm this results.

We showed that the frequencies of the DD genotype and the D allele of ACE I/D gene polymorphism are higher in children with parental history of premature CAD. This results may be associated with an increased risk for development of atherosclerosis. Family history is the most significant independent risk factor for CAD.

The study protocol was approved by the Local Ethical Committee of Celal Bayar University, and informed written consent was obtained from all participants. This study was funded by Celal Bayar University.

**Additional information:**

In addition to ACE I/D gene polymorphism, glycoprotein IIIa, factor V G1691A, factor V H1299R, prothrombin G20210A and apolipoprotein E polymorphism in children with family history of premature coronary artery disease.

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1. de Albuquerque FN, Brandão AA, da Silva DA, Mourilhe-Rocha R, Duque GS, Gondar AF, et al. Angiotensin-converting enzyme genetic polymorphism: its impact on cardiac remodeling. Arq Bras Cardiol. 2014;102(1):70-9.

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References

Reply

The insertion<sup>1</sup>/deletion (I/D) polymorphism in the gene for angiotensin converting enzyme (ACE) has been studied in different clinical scenarios beyond heart failure (HF), which is described in this article, such as hypertension<sup>1</sup>, atrial fibrillation (AF)<sup>2</sup>, and coronary heart disease (CHD)<sup>3</sup>. In all these scenarios, there appears to be a relationship between the DD genotype and poor clinical outcome, albeit with some controversy due to the small number of patients.

Typically, the outcomes used in these small studies are surrogate markers such as echocardiographic parameters (original article) or left ventricular hypertrophy, for example. In other works, it is only possible to detect the relationship between genotypes and incidence of the disease studied<sup>2</sup>.

In the case of atherosclerosis, because of the prevalence and importance of CHD, there are a greater number of publications such as those presented in letters to the editor on the various types of atherosclerosis: subclinical or clinical. Our work<sup>4</sup>, in particular, focused only on patients with nonischemic HF, and it was possible to observe the association between poor Echo profile and the DD genotype.

More recently, it has been described that HF physiopathology and Renin Angiotensin activity is actually linked to a polygenic heritage. The simultaneous study of multiple genetic polymorphisms (GPs) in the same population has identified that only combinations of genotypes have been associated with clinical and/or echocardiographic outcomes<sup>5,6</sup>.

Therefore, it is likely that a panel of genetic markers would be more efficient in detecting more severely ill individuals than isolated GPs. Since then, our group has been focusing on this kind of analysis, and preliminary data suggest an association between a genetic panel, which included polymorphisms of the angiotensin-converting enzyme, beta adrenergic receptor type 1, nitric oxide synthetase, and Angiotensin II, and clinical outcomes. The continuation of this study, which is already underway, with more patients may help clarify this issue.

Sincerely,

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