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Prognostic Value of Different Allelic Polymorphism of Aldosterone Synthase Receptor in a Congestive Heart Failure European Continental Ancestry Population

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Aldosterone synthase (CYP11B2) is as an 9-exon gene on chromosome 8q22 and exists as a common single nucleotide polymorphism C−T transition for position −344. The aim of this study was to assess the −344T/C polymorphism of the aldosterone synthase promoter in a European continental ancestry congestive heart failure (CHF) population.

Methods. Patients discharged after an acute decompensation were enrolled and underwent echocardiography, determination of BNP, evaluation of non-invasive cardiac outputs and determination of −344 T/C SNP in the aldosterone synthase gene.

Results. 175 patients (137 male; age 69.9 ± 10.2 years) were enrolled. The genotype distribution of −344 T/C SNP demonstrated a TT genotype in 61 patients (34.9%), CT in 80 (45.7%) and finally CC in 34 (19.4%) CHF patients. According to presence of C allele, CHF patients were divided into C group (−CT/CC genotype, 114 subjects) and T Group (−TT genotype, 61 subjects). The two groups did not differ in term of age, non-invasive cardiac output at rest, creatinine level or end-systolic or diastolic left ventricle diameter, LVEF and BNP. In group C patients in comparison than in group T a higher degree of disability (Barthel Index $p = 0.004$), NYHA class ($p = 0.02$) and a lower cardiac index ($p = 0.01$) emerged. Moreover, the two groups showed a similar clinical outcome (death for any cause/hospital readmission for CHF) at 48 month follow-up ($p = 0.16$; log-rank 1.99).

Conclusions. In European continental ancestry patients the C allele (CC or CT) at −344T/C SNP in the aldosterone synthase gene does not significantly influence clinical prognosis of CHF. © 2017 IMSS. Published by Elsevier Inc.

Key Words: Congestive heart failure, Polymorphism, Aldosterone synthase receptor.

Introduction

Risk stratification in patients suffering chronic congestive heart failure (CHF) has usually based on a variety of clinical and laboratory variables. Indeed, several prognostic parameters have been identified, including age, New York Heart Association (NYHA) class, renal function, comorbidity such as atrial fibrillation, diabetes mellitus and ischemic heart disease (1). In acute decompensated heart failure (ADHF) episodes, the degree of renal dysfunction and arterial hypotension easily stratified patients with worst clinical outcome (2). A single determination of Brain Natriuretic Peptide (BNP) plasma level represents a reliable risk stratification procedure and its increase is considered a sensitive diagnostic marker of left ventricular dysfunction (3,4).

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Blockade of the aldosterone receptor has been shown to improve heart failure outcomes. Aldosterone synthase (CYP11B2) is a 9 exon gene occurring on chromosome 8q22 and a common single nucleotide polymorphism (rs1799998) C−T transition for position −344 has been described (5). The C allele binds the steroidogenic transcription factor 1 (SF-1) four times more than the allele T and determined an increased aldosterone production (6). The CYP11B2 promoter polymorphism seemed to be correlated to arterial hypertension (7), left ventricular size and mass in healthy subjects (8) and in hypertensive patients (9). The experiences about influence of CYP11B2 promoter polymorphism on morbidity and mortality of coronary artery disease obtained conflicting results (10,11). In African Americans CHF patients the aldosterone synthase promoter −344C allele was associated with elevation of aldosterone plasma level and poorer clinical prognosis (12) and was an independent predictor of atrial fibrillation (13).

The aims of this study were to assess: a) the different allelic distribution of −344T/C polymorphism of the aldosterone synthase promoter in a European continental ancestry heart failure (CHF) population; b) the role of −344T/C polymorphism in predicting mid-term clinical outcome in CHF patients discharged after an ADHF episode.

Methods

Patients

This prospective cohort study, approved by the local ethics committees, included patients admitted into the Heart Failure Unit from April 2008 up−August 2014. All CHF subjects (individuals from Northern Italy) discharged after an acute episode of cardiac decompensation were enrolled in an out-patient clinic follow-up. Patients were classified as having CHF according to the criteria commonly accepted in literature (14), namely the presence of 2 major criteria or 1 major criterion + 2 minor criteria according to the Framingham score and a NYHA functional class II, III, or IV, due to an exacerbation of symptoms with at least 1 class deterioration. The presence of inadequate echo images or no adherence to the therapy and disagreement with the periodical follow-up were considered exclusion criteria. All patients underwent a clinical examination, a 12 lead electrocardiogram, plasma determination of BNP, water composition (on admission and at discharge), 6 min walk test (6MWT), non-invasive cardiac output and a transthoracic echocardiogram within 48 h upon hospital discharge. The criteria for discharging CHF patients were the following: a) subjective improvement on the basis of NYHA class, with no orthopnoea; b) 100 <SBP <120 mmHg; c) heart rate <100 bpm; d) pulse oxymetry in ambient air >90%; e) diuresis >1000 mL/d (14). Serum creatinine was checked on clinical stability. According to the study protocol, CHF out-patients were checked at 3 and 6 months after hospital discharge. In case of worsening of the clinical status (worsening dyspnoea, body weight increase or oedema, cardiac arrhythmias), a clinical control was provided. The therapy prescribed in those patients included angiotensin converting enzyme inhibitors (enalapril, ramipril), angiotensin receptor blockade (valsartan) in case of enalapril/ramipril intolerance, β-blockers (bisoprolol), digoxin, loop diuretic and spironolactone at low dose. For β-blockers, angiotensin converting enzyme inhibitors and angiotensin receptor blockade, the patients' maximum tolerated dose was used, after an adequate titration period.

Doppler Echocardiography

Echocardiograms were performed with a Vivid 7 computed sonography system (GE Medical Systems, Waukesha, Wisconsin, USA) according to the recommendations of the American Society of Echocardiography (15). Two-dimensional apical 2- and 4-chamber views were used for volume measurements; LVEF was calculated with a modified Simpson's method using biplane apical (2- and 4 chamber) views. The LV end-diastolic volume and the LV end-systolic volume were recorded. All the echo examinations were performed by expert operators blinded to the results of BNP assay; the intra-observer variability in the evaluation of LVEF was found to be <5%. Echocardiographic measurements including LV end-diastolic diameter, and the diastolic thickness of the ventricular septum and the posterior LV wall were determined according to the American Society Echocardiography recommendations (12). Systolic dysfunction was defined as a level of LVEF<50%. The definition of restrictive filling pattern (grade 3) was a predefined modification of classifications used in prior studies (16): E/A >2, DT <150 msec, S/D ratio <1, and AR >35 cm/sec. All these criteria should be verified to define the restrictive filling pattern. The other diastolic filling patterns were classified as: grade 1 (abnormal relaxation) when E/A<1 with a DT>240 ms; grade 2 (pseudonormal) when E/A between 0.75−1.5, DT between 160−240 ms and finally E/Ea>15 (16). The Doppler sample was set 1−2 mm under the free edges of the mitral valve using the apical 4 chamber projection; an average of 5 beats was considered. In patients suffering from atrial fibrillation at the time of the echocardiogram, the diastolic function was classified as: 1) restrictive pattern (DT <150 msec) or 2) indeterminate (DT >150 msec). <150 msec, S/D ratio <1, and AR >35 cm/sec. All these criteria should be verified to define the restrictive filling pattern. The presence of this diastolic pattern with a LVEF≥50% was defined as an isolated diastolic dysfunction. The tricuspid annular plane systolic excursion (TAPSE) was measured in a four-chamber view by placing the 2D cursor at the tricuspid lateral annulus and measuring the distance of systolic annular RV excursion along a longitudinal line