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Pathogenic role of renin-angiotensin-aldosteron gene polymorphism in hypertensive heart failure women

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Abstract

Arterial hypertension is still a major public health issue worldwide. Under these circumstances, researchers are making every effort to identify risk factors for essential hypertension including gene polymorphism in the renin-angiotensin-aldosterone system. The study was performed on 40 females admitted in the Rehabilitation Hospital Cluj-Napoca, Cardiology Department. According to the 2012 European Society of Cardiology criteria, 20 women were diagnosed with hypertension and chronic heart failure NYHA III-IV class, and 20 with no cardiovascular disease [control group]. In our study, 65% of the patients had more than one potentially pathogenic mutation (heterozygous or homozygous) at the same time, and 7% only homozygous gene polymorphism associations: TT+DD+AA (2 patients), DD+CC (3 patients), and TT+DD (2 patients). As far as the controls were concerned, 25% had potentially pathogenic gene polymorphism and 15% homozygous associations: DD+CC (2 women) and TT+DD+ CC (1 woman). All the patients enrolled in the study received renin-angiotensin-aldosterone system inhibitors: 80% converting enzyme inhibitors and 20% sartans. In conclusion, the presence of gene polymorphism in the renin-angiotensin-aldosterone system in women may play a significant part in high blood pressure pathogenesis subsequently leading to heart failure.

Keywords: renin-angiotensin-aldosteron gene polymorphism, hypertension, heart failure, women

Introduction

Arterial hypertension is still a major public health issue worldwide. It is the leading risk factor for cardiovascular death [1]. Therefore, the World Health Organization aligning with the World Heart Association objectives has made a commitment to reduce cardiovascular mortality by 25% by 2025 and this target be also achieved by a 30% decrease in arterial hypertension incidence [2].

The EUROASPIRE IV survey has determined that, in Europe, high blood pressure incidence is 43 % (42 % in men and 44% in women) [3].

According to the SEPHAR II survey, arterial hypertension incidence in Romania is 40.1 % [4]. The same study has called attention to the fact that even though most patients with hypertension receive antihypertensive medication, only

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25% have blood pressure below 140/90 mmHg [4]. Values recommended by current guidelines [5, 6].

Essential hypertension plays a major part in many cardiovascular complications most important of which are stroke, heart failure, ischemic cardiomyopathy, and death. High blood pressure in heart failure patients occurs mainly in women and elderly patients and it is an aggravating factor [7].

Under these circumstances, researchers are making every effort to identify risk factors for essential hypertension, one of which is undoubtedly the gene factor. A significant part in the pathogenesis of essential arterial hypertension is played by gene polymorphism in the renin-angiotensin-aldosterone system [8].

The same gene mutations are often responsible for heart failure as well [8, 9].

The present study aims at identifying gene polymorphism in the aldosterone of angiotensin II converting enzyme and AT1 receptor in women with arterial hypertension and heart failure.

Material and methods

The study was performed on 40 females admitted in the Rehabilitation Hospital Cluj-Napoca, Cardiology Department. According to the 2012 European Society of Cardiology criteria, 20 women were diagnosed with hypertension and chronic heart failure NYHA III-IV class, and 20 with no cardiovascular disease [control group]. All the patients were assessed for the presence of cardiovascular risk factors. As cardiovascular risk factors we analyzed body weight, smoking habits, glycemia, hypertension, serum lipid fractions. Blood pressure was measured according to standard protocol as the mean of two readings after the participant was at rest for 5 min in a sitting position.

After DNA isolation from blood leukocytes, M235T, T174M, and A1166C were identified using the PCR amplification reaction followed by enzymatic digestion with restriction endonucleases, (PCR–RFLP analysis). The local institutional Ethics Committee approved the study and all participants gave their written informed consent.

Statistical analysis was carried out using SPSS for Windows 16.0 and MedCalc 10.3.0.0 software programs. The analysis of the differences between qualitative variables was performed by using the χ^2 test. Mean differences among continuous qualitative variables were evaluated with the Student's t-test (unpaired and paired), while nonparametric tests (Mann–Whitney U) were used to assess distribution variables that did not comply with normal conditions. A value of $P< 0.05$ was deemed statistically significant.

Results

The mean age of the hypertensive patients was 73.25 ± 7.83 years. The presence of cardiovascular risk factors in these women was summarized in table 1. The mean age of the women in the control group was 46.6 years.

The presence of gene polymorphism in the patients with heart failure and hypertension and in the controls was summarized in table 2, namely 3.

We should mention that 65% of the patients had more than one potentially pathogenic mutation (heterozygous or homozygous) at the same time, and 7% only homozygous gene polymorphism: TT+DD+AA (2 patients), DD+CC (3 patients), and TT+DD (2 patients) - figure 1.

As far as the controls were concerned, 25% had potentially pathogenic gene polymorphism and 15% homozygous associations: DD+CC (2 women) and TT+DD+ CC (1 woman) - figure 1.

All the patients enrolled in the study received renin-angiotensin-aldosterone system inhibitors: 80% converting enzyme inhibitors and 20% sartans.

Discussions

For both sexes, arterial hypertension is a major risk factor for ischemic cardiomyopathy, heart failure, and stroke [10].

Table 1. Main features of hypertension heart failure patients.

Variables	Heart failure patients (23 patients)
Age [years]	73.25 ±7.83
BMI [kg/m^2]	29.50±11.41
Glycemia [mg/dl]	100.5±23.31
Total Cholesterol [mg/dl]	165.75±34.23
LDL-Cholesterol [mg/dl]	103.62±22.14
HDL-Cholesterol [mg/dl]	35.87±7.8
Triglycerides [mg/dl]	131.37±59.37
Diabetes [%]	20.9 %
ACEI orARB's	80%

Table 2. Gene polymorphism in patients with hypertension and heart failure.

Gene polymorphism	M235T	T174M	ACE-I/D	AGTR1-A/C
Negative (%)	MM - 25 %	TT – 65%	II – 15 %	CC- 40%
Heterozygote %)	TM - 25 %	MT – 35%	ID – 45%	AC – 45%
Homozygote (%)	TT - 50 %	MM - -	DD – 40%	AA – 15%

Table 3. Gene polymorphism in women without cardiovascular pathology.

Gene polymorphism	M235T	T174M	ACE-I/D	AGTR1-A/C
Negative (%)	MM - 75 %	TT – 90%	II – 25 %	CC- 60%
Heterozygote (%)	TM - 15 %	MT – 10%	ID – 40%	AC– 25%
Homozygote (%)	TT - 10 %	MM - -	DD – 35%	AA – 15%

The INTERHEART survey determined that HBP is associated with a 36% cardiovascular risk in women as compared to 19% in men [11].

Women in developing countries have mean systolic blood pressure values higher than male subjects. Similarly, in these countries women have higher blood pressure than their counterparts in developed countries. HBP incidence increases in both sexes with age, but between 45-54 years of age the increase is more significant in women. In subjects younger than 35 years of age, hypertension is definitely recurring more often in men than in women [12]. In the SEPHAR II study the majority of hypertensive subjects were females (54.9%), mean age 57.42 ± 13.38 years, coming from the South region (17.8%), living in urban areas (59.5%) and aware of their condition (69.5%), associating most often other 4 cardiovascular risk factors [4].

Irrespective of age, HBP in women is associated with a 3-5 times higher risk of coronary disease [10, 13]. Even blood pressure values at threshold (140/90 mm Hg) or slightly higher may contribute to exacerbate endothelial dysfunction

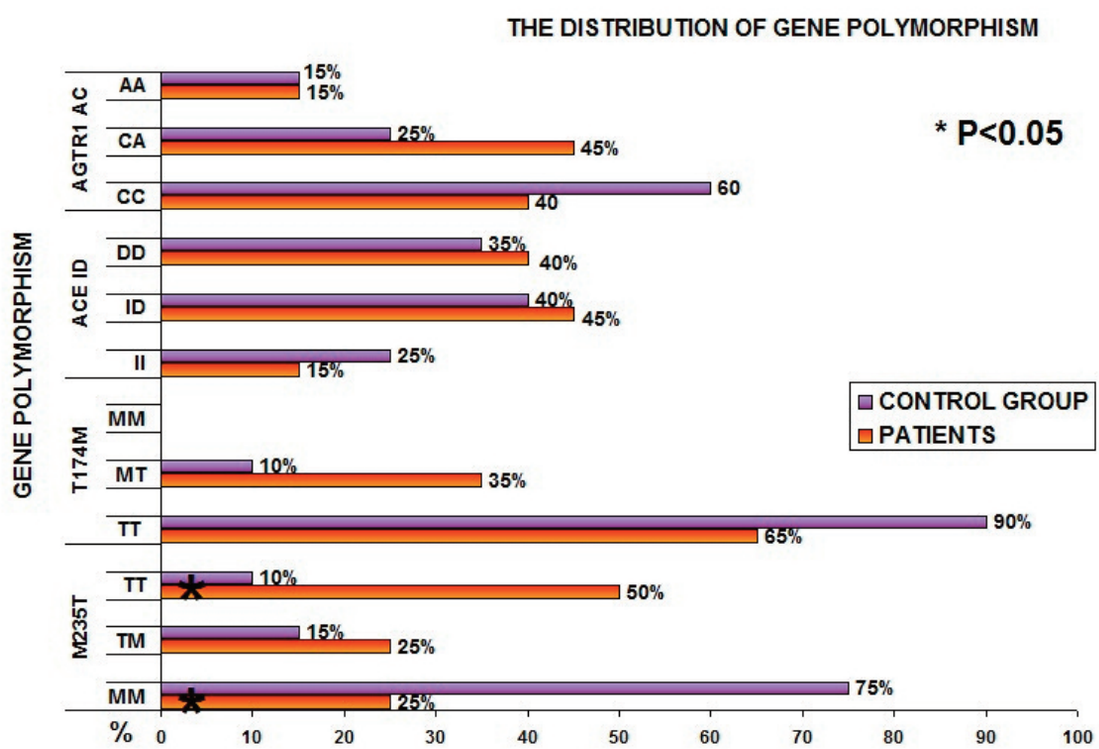

Figure 1. The distribution of gene polymorphism.

leading to more severe complications in women than in men [14].

There are several differences between sexes regarding arterial hypertension and its associated risk factors [15]. They can be ascribed to a great extent to gene factors (chromosome X or Y), namely the genes of the steroid hormone biosynthesis and metabolism [15].

Consequently, the sex-determining Y chromosome responsible for male characteristics could be as well responsible for the gender differences in blood pressure values and response to stress [15] by activating the sympathetic nervous system, decreasing norepinephrine turnover, and modulating the response to salt intake [15]. At the same time, the X chromosome, present in both sexes, may play a significant part in hypertension and other cardiovascular diseases (such as cardiovascular malformations, Turner syndrome, and dilated cardiomyopathy) [15].

The renin-angiotensin-aldosterone system has a major role in regulating blood pressure by influencing salt-water homeostasis and vascular tone. Angiotensin II exerts its main effects by means of its receptors AT1 and AT2. Arterial hypertension, chiefly in women, may be the result of gene polymorphism in the genes that carry the code to produce the receptors [15].

There are many studies dedicated to part played by gene polymorphism in the renin-angiotensin-aldosterone system in the pathogenesis of HBP [16–18] as well as of CHF [19–21].

Two molecular variants of the angiotensinogen gene, M235T and T174M, have been linked individually to elevated levels of plasma angiotensinogen, one encoding threonine (T) instead of methionine (M) at position 235 (M235T) and the other encoding methionine rather than threonine at position 174 (T174M). They have been proved to be associated with increased activity of the RAAS, and consequently, with increased severity and poor prognosis in hypertensive patients. The incidence of potentially pathogenic M235T gene polymorphism has been reported in 75% of the women with HBP and CHF as compared to only 25% of the women without cardiovascular pathology. On the contrary, in what concerns the T174M gene mutations, a much lower percentage has been reported both in hypertensive and healthy women - 35% vs. 15%.

Rigat et al. have identified gene polymorphism within intron 16 consisting in the presence or absence of a 287 base-pair fragment [22]. The presence of the respective fragment defines the I (insertion) allele and its absence the D (deletion) allele. Depending on the allelic combination there are three converting enzyme genotypes: II, DD, and ID [22].

Serum levels of the converting enzyme depend on the ACE I/D gene polymorphism, higher levels characterizing the DD genotype also associated with the highest levels of cell activity [23]. Raynolds et al. have been the first to report a connection between ACE gene polymorphism and heart failure, chiefly in patients with dilated and ischemic cardiomiopathy [24]. The explanation would be the elevation of converting enzyme levels in these patients and the involvement of the RAAS in activating mechanism that determine cardiac remodeling [24]. McNamura has emphasized that the DD mutation occurs in a third of the population reported with higher CE levels [25]. As for the women enrolled in our study, potentially pathogenic gene polymorphism has been reported in 85% of the patients, and in an equally high percentage, 75%, in the healthy controls. Undoubtedly, the latter would have to be carefully monitored to diagnose as soon as possible high blood pressure.

It has been demonstrated that the AT1 receptors, present in vascular smooth muscle cells and myocardium, which are responsible for most of the CE effects, have gene polymorphism. Three AT1 receptor genotypes have been identified depending on the nucleotide 1116 in the RNA sequence responsible for these receptors: CC, AA, and AC [8]. Among them, the CC homozygous genotype is most often associated with left ventricular hypertrophy and high risk of myocardial infarction [26, 27]. The available information on this type of mutation in heart failure patients is scanty in the literature in the field. Sixty percents of the patients enrolled in our study had this type of potentially pathogenic gene polymorphism, and 40% of the healthy controls.

It has also been reported an association between the DD genotype and AGT gene polymorphism, which increases the risk of premature ischemic cardiomyopathy [28].

The AT1 CC genotype is associated with the converting enzyme DD genotype, resulting in a very low level of converting enzyme, which explains the proclivity of hypertensive patients for development of earlier and more severe cardiovascular complications at similar blood pressure rates [26, 29].

At the same time, it has been demonstrated that patients with low cardiovascular risk have a strong synergistic relationship between the two CE and AT1 gene polymorphisms: the DD+AC association results in a 7.03 risk of myocardial infarction, and the DD+CC association, in a 13.3 risk [27].

In our study, 65% of the patients had more than one potentially pathogenic mutation (heterozygous or homozygous), and 7% only homozygous gene polymorphism associations: TT+DD+AA, DD+CC, and TT+DD.

It has been reported that hypertensive men have higher levels of ACE/AngII, whereas in women before menopause prevails the association CE2/Ang (1-7)MasR and AT2 with no damaging effects[30]. A series of new studies have demonstrated that women with preeclampsia have RAAS potentially pathogenic gene polymorphism associations, chiefly AT1 R1166AC and ACED [31], and also AGTM235T or multiple associations [32, 33].

As far as the treatment is concerned, blood pressure values are kept under control to levels recommended by guidelines to a lesser extent in women (chiefly with diabetes or over 65 years of age) than in men . Women receive treatment to a lesser extent even after being diagnosed with arterial hypertension. Whereas blood pressure treatment and control rates have increased in men with 9.8%, namely 15.3%, they have maintained rather constant levels in women (increasing only with 1.9, namely 0.5%). The NHANES (National Health and Nutrition Examination Study) survey has reported alarmingly rising HBP rates in women in the USA under the circumstances in which the prescription of antihypertensive medication has increased for both sexes. In our study, all the women with high blood pressure and heart failure have received converting enzyme inhibitors and sartans according to the recommendations of the guidelines.

In conclusion, the presence of gene polymorphism in the renin-angiotensin-aldosterone system in women can play a significant part in high blood pressure pathogenesis and in the subsequent development of heart failure.

Conflict of interests

The authors confirm that there are no conflicts of interest.

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