THE ROLE OF ANGIOTENSIN-CONVERTING ENZYME OF I/D GENE POLYMORPHISM IN THE DIAGNOSIS OF CHRONIC HEART FAILURE WITH ANEMIA OF VARIOUS ETIOLOGIES

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ABSTRACT

This paper examines the rate of occurrence of the I/D polymorphism of the enzyme gene that converts angiotensin in patients with anaemia of various etiologies of chronic heart failure and the importance of polymorphism in the development of the disease. The allele and genotypes of the angiotensin-converting enzyme polymorphism allele and genotypes were compared with the prevalence of chronic heart failure in iron deficiency anaemia, chronic disease, and renal anaemia, while the D allele and DD genotype in the renal anaemia group were iron deficiency anaemia, respectively (64.1 vs 49), 1% (r = 0.05) and (47.1 vs 36) 11.1% (r = 0.3), chronic disease anaemia compared to the group (62.5 vs 49) 13.5%, (r <0.05) and (45.5 vs 36) were 9.5% (r = 0.35) lower I allele and genotype II in the renal anaemia group corresponded to 15% in the group of iron deficiency anaemia (51 vs 36) and 20.2% (r <0.05) (r <0.05) in the group of chronic diseases, respectively. (37.5 vs 51) 13.5% and (25 vs. 39) 14% (r <0.05). Patients with CHF carrying the genotype II of the angiotensin-converting enzyme gene I/ D polymorphism have a significantly higher probability of developing renal anaemia, and the D allele of this polymorphism has a protective effect against the development of renal anaemia.

Keywords: chronic heart failure, anaemia, angiotensin-converting enzyme gene.

I. INTRODUCTION

It is known that the study of polymorphisms of genes influencing the pathogenesis, course, and prognosis of chronic heart failure (CHF) is one of the important tasks of medical genetics. Genetic analysis allows predicting the consequences of the disease and approaching individual treatment for each patient [4]. In recent years, the development of various hemodynamic phenotypes of CHF and the role of angiotensin-converting enzyme (ACE) gene polymorphism in left ventricular remodelling have been studied in many studies [3,7]. Also, according to meta-analyzes of scientific studies on the importance of polymorphism of this gene in the development of anaemia, the discrepancies in the data, the degree of occurrence of polymorphisms of this gene in different regions, especially in Europe and Asia, make it necessary to continue research. confirms [1,3,5].

In the literature review, some scientific studies are devoted to the role of ACE gene polymorphism in developing different nationalities and diseases, but data on this gene polymorphism in patients with CHF anaemia are insufficient [2]. Indeed, it can be concluded that today the role of ACE gene polymorphism in the course of anaemia of various etiologies, needed for large-scale research to study its impact on the development, course and prognosis of the disease [6]. This, in turn, indicates the need to continue research on this issue.

The aim of the research

To study the rate of occurrence of CHF with an ACE gene I/D polymorphism in patients with anaemia of various etiologies.

II. MATERIALS AND METHODS

The study conducted on patients treated in the cardiology and cardio rehabilitation departments of the Tashkent Medical Academy multidisciplinary clinic in 2017-2020. DNA isolation and analysis of polymorphic gene

markers performed in the biotechnology laboratory of the Center for Advanced Technologies of the Ministry of Innovation Development of the Republic of Uzbekistan. The study involved 203 Uzbek patients with chronic ischemic heart disease and hypertension. They divided into two groups: CHF anaemic and non-anaemic. According to the ferrokinetic indicators, the group of patients with chronic anaemia divided into the following 3 groups: "Chronic heart failure with absolute iron deficiency", "Chronic heart failure + iron deficiency disease" group; "CHF with chronic anaemia", "Chronic Heart + Chronic Disease Anemia" group; "Chronic Heart Atherosclerosis + Renal Anemia" group with renal anaemia developed by renal dysfunction. The group "Chronic Heart Atherosclerosis + Iron Deficiency" consisted of 53 patients with absolute iron deficiency, with an average age of 63.4 ± 1.2, men 22 (41.5%) and women 31 (58.5%). The group "Chronic Heart Atherosclerosis + Chronic Disease Deficiency" with 68 patients with chronic heart failure, with an average age of 64.1 ± 0.9, men 33 (48.5%) and women 35 (51,4%). The "Chronic Heart Atherosclerosis + Renal Anemia" group, developed under the auspices of CHF renal dysfunction, consisted of 36 patients with an average age of 64.0 ± 1.2, 13 men (36.1%) and 23 women (63.9%) formed. The group of CHF patients without chronic anaemia was 46 patients with an average age of 64.2 ± 1.3, 27 men (58.6%) and 19 women (41.3%).

The control group consisted of 40 healthy volunteers of Uzbek descent. DNA isolated from lymphocytes in peripheral blood and analyzed based on a polymerase chain reaction (PCR) in molecular genetic testing. Population control provided with DNA samples (n=40) from healthy volunteer donors working at the Tashkent Medical Academy.

III. RESULTS

When determining the number of CHF with I/D polymorphisms of the ACE I, D and ID and DD genotypes II, ID and DD in patients with and without anaemia, their prevalence was 42.5, 40 and 17.5%, respectively, in the control group healthy people. However, CHF with anaemia and genotypes of polymorphism I/D found in 15.2% - II, 39.1% - ID and 45.7% - DD. In the control group, allele I of this I/D polymorphism was found in 62.5% of cases, allele D in 37.5% of cases, while in the control group, which did not have anaemia of CHF, these indicators found in 34.8% of cases D % of alleles I and 65.2% of allele D.

Allele D [χ 2 = 13.2; OR 3.125; 95% confidence interval CI - 1.67-5.83; P <0.001] and DD genotype [χ 2 = 8.0; OR 3.96; CI –1,455–10,774; P <0.005] Patients with CHD were 1.7 and 2.6 times more likely than the control group, respectively, with a significantly higher risk of developing the disease. Allele I [χ 2 = 13.18; OR - 0.32; CI is 0.17-0.60; P <0.001] and genotype II [χ 2 = 7.9; RR - 0.243; CI - 0.088 - 0.673; P = 0.005]. It was found that in patients with CHF and anemia, which is 1.8 and 2.8 times lower than in the control group, they have a reliable protective effect against the onset of the disease. No reliable correlation was found between genotype ID and the risk of developing CHF[χ 2 = 0.007; RR - 1.038; CI 0.434 2.485; P = 0.933].

When studying the genotypes and I/D alleles of the ACE gene polymorphism in patients with CHF anaemia, the prevalence of the disease in various anaemias were determined as follows:

DD genotype in patients of the CHF + IDD group compared with the control group [χ 2 = 8.89; OR - 4.2 CI -1.58-11.19; P <0.005] 2.6 and D allele [χ 2 = 13.0; OR 2.98; CI –1.63–5.44; P <0.001], which was 1.7 times more likely to be associated with a significantly higher risk of developing the disease. Genotype II and allele I in this group of patients were 2.2 [χ 2 = 6.18, which was more consistent with the indicators of the control group; RR - 0.31; CI was 0.124-0.78; P = 0.05] and 1.7 [χ 2 = 13.0; RR - 0.335; CI was 0.18-0.61; P <0.001] had a reliable protective effect on the onset of the disease. There was no significant correlation of genotype ID with patients of this group [χ 2 = 0.36; OR - 0.77; CI 0.33 - 1.8; P = 0.55].

ACE gene in patients with CHF + CA compared to a control group were 2.6 [χ 2 = 1.67; OR 3.95; . CI - 1.54 - 10.16; P <0.005] and 1.6 [χ 2 = 9.81; OR - 2.45; CI- 1.39-4.33); P <0.005], and this group was significantly more likely to develop the disease. Genotype II and allele I in patients of this group were 1.6 [χ 2 = 2.95, 0.49; CI 0.21-0.81; P = 0.086] respectively, compared with the control group and 1.5 [χ 2 = 9.81; RR - 0.41; CI 0.23 - 0.72; P <0.005] was equally low and had a significant positive effect on the onset of the disease. There was no significant association of genotype ID with this group of diseases [χ 2 = 1.67; RR - 0.58; CI 0.25-1.33; P = 0.2]

Genotype II of the ACE gene and allele I of CHF in patients with renal insufficiency were 1.6 [χ 2 = 4.45, OR - 2.71; CI - 1.06-6.89; P <0.05] and 1.2 [χ 2 = 4.19; OR - 2.1; CI - 1.03-4.3; P <0.05] respectively, compared with the control group and 1.2 [χ 2 = 4.19; OR - 2.1; CI - 1.03-4.3; P <0.05], and in their presence it was found that the likelihood of developing this anemia was quite high. In patients with genotype DD and allele D, CHF + RA values

were 1.6 [χ 2 = 0.62, OR - 0.59; CI = 1.16-2.21; P = 0.62] respectively, compared with the control group; and 1.7 [χ 2 = 4.19; OR = 0.48; CI 0.23-0.975; P = 0.05] decreased in the same way.

It was found that only the D-allele had a reliable protective effect in renal anaemia in patients with CHF. No significant correlation of genotype ID with this hemodynamic phenotype of the disease reported. [χ 2 = 2.77; OR - 0.43; CI is 0.156-1.18; P = 0.096].

When comparing the prevalence of alleles and genotypes of the I / D polymorphism of the ACE gene in CHF CA, IDD and RA (Table 1), the D allele and the DD genotype were 15.1% in group 3 compared with group 1 (64.1 versus 49), respectively 15,1% (r = 0.05) and (47.1 versus 36) 11.1% (r = 0.3), compared with group 2 (62.5 versus 49) 13.5% (r <0.05) and (36 versus 45.5) decreased by 9.5% (r = 0.35). Allele I and genotype II were 15% (r <0.05) and (18.8 versus 39) 20.2% (r <0.05), respectively, in group 3 (36 versus 51) and 3 (18.8 versus 39), respectively, Compared to group 2 (37,5 versus 51), 13.5% (r <0.05) and (25 versus 39) were 14% (r <0.05) significantly higher.

Table 1

I/D polymorphism of the ASE gene in hemodynamic phenotypes of chronic heart failure

Allele and genotype	Occurrence of alleles and genotypes,%		P	Occurrence of alleles and genotypes,%		P	Occurrence of alleles and genotypes,%		P
	CHF+ IDD group	CHF+CA group		CHF+CA group	CHF+RA group		CHF+IDD group	CHF+ RA group	
I	35,8	40,4	0,467	35,8	77,8	0,001	40,4	77,8	0,001
D	64,2	59,6	0,467	64,2	22,2	0,001	59,6	22,2	0,001
I/D	33,9	27,9	0,475	33,9	22,2	0,23	27,9	22,2	0,53
D/D	47,2	45,6	0,86	47,2	11,1	0,001	45,6	11,1	0,001
I/I	18,9	26,5	0,32	18,9	66,7	0,001	26,5	66,7	0,001

Statistically, the II genotype and I allele of the ACE gene I / D polymorphism showed a higher risk of renal anaemia in patients with CHF than the IDD and CA patients with CHF + RA. In contrast, the D allele [χ^2 = 4.19, OR– 0.48; CI- 0.23 - 0.975; P = 0.05], which had an aggressive character in CHF occurrence, showed a protective effect on the development of renal anaemia in patients with CHF.

AAF gene polymorphism studied in 157 patients with CHF anaemia and 46 patients without CHF anaemia, and the results compared with 40 healthy people of Uzbek descent. When the I/D polymorphism of the AAF gene in patients with CHF determined by the number of encounters of genotypes II, ID, and DD, their prevalence was 42.5, 40 and 17.5%, respectively, in the control group of healthy individuals. In the CHF anaemic group, the genotypes of I/D polymorphism were 15.2% - II, 39.1% - ID, and 45.7% - DD. In the control group, the I allele of this gene I/D polymorphism found in 62.5% of cases, and the D allele in 37.5% of cases, while patients with CHF anaemia, these results were 34,8 % in allele I and D allele was 65,2%.

When comparing the prevalence of alleles and genotypes of the AAF gene I/D polymorphism in CHF IDD, AC, and RA, the D allele and DD genotype in the CHF + RA group respectively in the CHF + IDD group were (64.1 vs. 49) 15,1% (r=0,05) and (47.1 vs. 36) 11.1% (r = 0.3), compared to the CHF + CA group (62.5 vs. 49) 13.5% (r <0.05) and (45.5 vs 36) decreased by 9.5% (r = 0.35). I allele and genotype II in the CHF + RA group were higher than in the CHF + IDD group (36 vs 51) 15% (r <0.05) and (18.8 vs. 39), 20.2% (r <0.05), CHF + CA were convincingly higher than the group (37.5 vs. 51) 13.5% (r <0.05) and (25 vs. 39) 14% (r <0.05).

Statistically, the II genotype and I allele of the ACE gene I/D polymorphism showed a higher risk of renal anaemia in patients with CHF than the IDD and CA in patients with CHF + RA. In contrast, the D allele [χ^2=

4.19, OR– 0.48; CI- 0.23 - 0.975; P = 0.05], which had an aggressive character in CHF occurrence, had shown to have a protective effect on the development of renal anaemia in patients with CHF.

IV. DISCUSSION

Studies showed that chronic administration of AAFI and ARA, the first line of drugs used to treat patients with CHF, could slow their erythropoiesis process and led to anaemia. In addition, a clinical study of 167 patients on hemodialysis found that those with the DD genotype had a significantly lower EP resistance index than those with the II or ID genotypes, regardless of all factors that may contribute to the development of anaemia [3].

Another study reported that patients with diabetes and CKD carrying the DD genotype of the ACE gene I/D polymorphism developed renal failure faster than those carrying other genotypes of this polymorphism, and mortality was higher in this group [4].

AAF gene polymorphism studied in 157 patients with CHF anaemia and 46 patients without CHF anaemia, and the results compared with 40 healthy people of Uzbek descent. When the I/D polymorphism of the AAF gene in patients with CHF determined by the number of encounters of genotypes II, ID, and DD, their prevalence was 42.5, 40, and 17.5%, respectively, in the control group of healthy individuals. In the CHF anaemic group, the genotypes of I/D polymorphism were 15.2% - II, 39.1% - ID, and 45.7% - DD. In the control group, the I allele of this gene I/D polymorphism found in 62.5% of cases, and the D allele in 37.5% of cases, while in the group CHF anaemia, allele I was 34,8% and 65,2%.of allele D.

When comparing the prevalence of alleles and genotypes of the AAF gene I/D polymorphism in CHF IDD, AC, and RA, the D allele and DD genotype in the CHF + RA group respectively in the CHF + group were (64.1 vs. 49) 15.1% (r=0.05) and (47.1 vs. 36) 11.1% (r = 0.3), compared to the CHF + CA group (62.5 vs. 49) 13.5% (r <0.05) and (45.5 36) decreased by 9.5% (r = 0.35). I allele and genotype II in the CHF + IDD group were (36 vs. 51) and 15% (r <0.05) and (18.8 vs. 39) 20.2% (r <0.05) higher than in the CHF + RA group CHF + IDD were convincingly higher than the group (37.5 vs. 51) 13.5% (r <0.05) and (25 vs. 39) 14% (r <0.05).

Statistically, the II genotype and I allele of the ACE gene I/D polymorphism showed a higher risk of renal anaemia in patients with CHF than the IDD and CA patients with CHF + RA. In contrast, the D allele [χ^2 =4,19; OR– 0,48; C.I.- 0,23 - 0,975; P=0,05] aggressive character CHF occurrence showed to have a protective effect on the development of renal anaemia in patients with CHF.

V. CONCLUSION

Hence, the results showed that patients with CHF maintaining the genotype II of the ACE gene I/D polymorphism had a significantly higher probability of developing renal anaemia. In contrast, the D allele of I/D polymorphism had a protective effect against the development of renal anaemia.

CONFLICT OF INTERESTS AND CONTRIBUTION OF AUTHORS

The authors declare the absence of obvious and potential conflicts of interest related to the publication of this article and report on the contribution of each author.

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