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ANALYSIS OF MTHFR GENE ALA22VAL POLYMORPHISM SIGNIFICANCE IN THE RISK OF MYOCARDIAL INFARCTION

Khamidov Diyorbek Abdullayevichyevich[1]
Musashaykhov Umidjon Husanovich[2]
Musashaykhova Shakhnoza Mamirbekovna[3]
Assistants of Andijan State Medical Institute, c. Andijan, Uzbekistan

ABSTRACT
As the assessment of the association between the Ala222Val polymorphism in the MTHFR gene in the study groups shows, the calculated relative risk of developing MI in patients with a history of COVID-19 increased when the Ala/Val , Val/Val genotypes and the Val allele were detected, and the risk of developing MI in patients without COVID -19 in history increased when an unfavorable Val allele and an unfavorable Ala/Val genotype were detected.
KEYWORDS: ***myocardial infarction, COVID-19, Ala222Val genetic polymorphism of MTHFR gene.***

1. INTRODUCTION

Over the past two years, the results of cohort studies, a number of reviews and descriptions of clinical observations on complications caused by the SARS-CoV-2 virus, in particular in the cardiovascular system, have been published. The development of cardiovascular disorders exacerbated the severity of the patients' condition and increased the risk of mortality. For example, doctors in Italy reported a case of a 53-year-old patient whose clinical manifestations of COVID-19 were severe pericarditis with fever rather than pneumonia [6, p. 162; 3, p. 683]. In patients who died from COVID-19, biomarker levels before death were 12 times higher in the presence of morphological signs of myocardial damage than in their absence[5, p. 2403].

An increase in biomarker values is a sign of an unfavorable outcome of an existing disease. Undoubtedly, further research is needed on the diagnostic and prognostic role of biomarkers of myocardial stress in COVID-19. To this end, we studied the role of the Ala222Val polymorphism in the MTHFR in the risk of myocardial infarction (MI) in patients with a history of COVID-19 viral infection and in patients who did not have a history of transferred COVID-19.

2. PURPOSE OF THE STUDY

To study and evaluate the contribution of the Ala222Val polymorphism in the MTHFR gene to the risk of myocardial infarction (MI) in patients with a history of COVID-19 viral infection and in patients who did not have a history of COVID-19.

3. MATERIAL AND METHODS OF RESEARCH

In a specialized center for the treatment of patients infected with COVID-19 in the Andijan branch of the Republican Specialized Scientific and Practical Medical Center for Cardiology, in the cardiology department of the Andijan Regional Multidisciplinary Center and in the Andijan branch of the Republican Scientific Center for Emergency Medical Care, clinical and laboratory materials were collected from patients being treated for cardiovascular disease. In particular, patients with myocardial infarction were involved in the study. These patients were divided into two groups: patients with myocardial infarction with a history of COVID-19 viral infection and patients with myocardial infarction without a history of viral infection with COVID-19. In total, 94 patients with myocardial infarction aged over 18 years were involved in the study. Of them:

- The first group - 53 patients with myocardial infarction who had a history of viral infection with COVID-19;
- The second group - 41 patients with myocardial infarction who did not have a history of viral infection COVID-19
- The third group - a control group of 90 conditionally healthy donors.

Statistical processing of the results was performed using the standard software package OpenEpi V.9.2. Analysis of the deviation of empirical genotype frequencies from the theoretically expected Hardy–Weinberg distribution was carried out using the Statistica software package.

4. THE RESULTS OBTAINED AND THEIR DISCUSSION

An assessment of the level of association of the Ala222Val polymorphism in the MTHFR gene in patients with COVID-19 associated MI and controls showed that the proportion of the Ala allele and the favorable Ala/Ala genotype in comparison with the control group was

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significantly lower and amounted to 77.5% versus 85.0% and 56.6% versus 73.3%. All this indicates a protective effect against the development of myocardial infarction in patients with COVID-19. Statistical data processing revealed a significant increase in the frequency of the Val allele in patients with COVID-19 associated MI compared with conditionally healthy donors. The detection of an unfavorable Val allele in patients with a history of COVID-19 increased the risk of MI by 1.9-fold compared with the control group (25.5% vs. 15.0% at $\chi2$=4.8; P=0 .05; OR=1.9; 95%CI: 1.07–3.5). The frequencies of Ala/Val, Val/Val genotypes Ala222Val in the MTHFR gene in the studied groups of patients with COVID-19 associated MI and controls were: 35.8%, 7.5% versus 23.3% and 3.3%, respectively. There was a trend towards the risk of MI in patients with a history of COVID-19 in the presence of Ala/Val, 1.8-fold ($\chi2$=2.6; P=0.2; OR=1.8; 95% CI:0 .88–3.85) and Val/Val, 2.4 times ($\chi2$=1.3; P=0.3; OR=2.4; 95%CI: 0.53–10.58) (Tab. 1).

The results of the analyses show that the presence of these genotypes of the JAK2V617F gene does not increase the chance of detecting ET compared to patients with PMF ($\chi2$=0.1; OR=0.9; 95%CI:0.4-2.03; p=0.9 and $\chi2$=0.1; OR=1.1; 95%CI:0.49-2.48; p=0.9) (Table 1).

Table 1. Association between the Ala222Val polymorphism in the MTHFR gene in groups of patients with COVID-19 associated MI and controls.

Alleles and genotypes	Number of examined alleles and genotypes				$\chi2$	p	OR	95%CI
	COVID-19 associated MI		Control group					
	n	%	n	%				
Ala	79	74,5	153	85,0	4,8	p = 0,05	0,5	0,29 - 0,93
Val	27	25,5	27	15,0	4,8	p = 0,05	1,9	1,07 - 3,5
Ala/Ala	30	56,6	66	73,3	4,2	p = 0,05	0,5	0,23 - 0,97
Ala/Val	19	35,8	21	23,3	2,6	p = 0,20	1,8	0,88 - 3,85
Val/Val	4	7,5	3	3,3	1,3	p = 0,30	2,4	0,53 - 10,58

In the studied subgroup of patients with MI without a history of COVID-19 virus infection and in the control group, the frequency of the wild Ala allele was 75.6% versus 85.0%. And the proportion of the mutant Val allele was 24.4% and 15.0%, respectively. The results of the study showed an insignificant decrease in the frequency of the favorable Ala allele (at $\chi2$=3.4; P=0.1; OR=0.5; 95% CI: 0.29–1.04) and a trend towards an increase in the proportion of the mutant allele Val in patients with MI without a history of COVID-19 virus infection compared with conditionally healthy donors (at $\chi2$=3.4; P=0.1; OR=1.8; 95% CI: 0.96–3.48). When an unfavorable Val marker was detected, the risk of developing MI increased by 1.8 times. In the subgroup of patients with MI without a history of COVID-19 virus infection and in the control group, the distribution of Ala/Ala, Ala/Val, Val/Val Ala222Val genotypes in the MTHFR gene was: 53.7%, 43.9% and 2.4% against 73.3%, 23.3% and 3.3% respectively. These studies showed a significant decrease in the proportion of the wild Ala/Ala genotype compared with the control group (at $\chi2$=4.9; P=0.05; OR=0.4; 95% CI: 0.2–0.9), which indicates a protective effect of this genotype against the development of MI. A significant increase in the frequency of the unfavorable marker Ala/Val ($\chi2$=5.7; P=0.03; OR=2.6; 95% CI: 1.18–5.58) was found in the subgroup of patients with MI without COVID-19 virus infection. 19 in history compared with the control group. When an unfavorable marker Ala/Val was detected, the risk of developing MI increased by 2.6 times An insignificant decrease in the mutant marker Val/Val ($\chi2$=0.1; P=0.8; OR=0.7; 95% CI: 0.07–7.12) was found in the subgroup of patients with MI compared with the control group. When carrying the Val/Val mutant genotype, there was no risk of MI (Table 2).

Table 2. Association between the Ala222Val polymorphism in the MTHFR gene in groups of patients with myocardial infarction without a history of COVID-19 virus infection and controls.

Alleles and genotypes	Number of examined alleles and genotypes				$\chi2$	p	OR	95%CI
	MI without COVID-19		Control group					
	n	%	n	%				
Ala	62	75,6	153	85,0	3,4	p = 0,10	0,5	0,29 - 1,04
Val	20	24,4	27	15,0	3,4	p = 0,10	1,8	0,96 - 3,48
Ala/Ala	22	53,7	66	73,3	4,9	p = 0,05	0,4	0,2 - 0,9
Ala/Val	18	43,9	21	23,3	5,7	p = 0,03	2,6	1,18 - 5,58
Val/Val	1	2,4	3	3,3	0,1	p = 0,80	0,7	0,07 - 7,12

The distribution frequency of Ala222Val alleles in the MTHFR gene in groups of patients with MI without a history of COVID-19 virus infection and with COVID-19 associated MI: (wild) Ala allele 74.5% vs. 75.6% and

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(unfavorable) Val allele 25, 5% versus 24.4% respectively. The results showed that the wild Ala allele and the unfavorable Val allele were found in insignificant amounts in both groups of patients (at $\chi2$=0.0; P=0.9; OR=0.9; 95% CI: 0.48–1.84 and $\chi2$=0.0; P=0.9; OR=1.1; 95% CI: 0.54–2.06). Calculation analyzes showed an insignificant increase in the number of favorable Ala/Ala genotype (56.6% versus 53.7% at $\chi2$=0.1; P=0.8; OR=1.1; 95% CI: 0.5–2 56) and a non-significant decrease in the frequency of the unfavorable marker Ala/Val (35.8% versus 43.9% at $\chi2$=0.6; P=0.5; OR=0.7; 95% CI: 0.31–1, 64) in the group of patients with COVID-19 associated MI than in the group of patients with MI without a history of COVID-19 virus infection. A trend towards an increase in the frequency of the unfavorable Val/Val genotype was revealed (7.5% versus 2.4% with $\chi2$=1.2; P=0.3; OR=3.3;). In the group of patients with a history of COVID-19, when this marker was detected, the risk of developing MI increased 3.3 times more than in the group of patients without a history of COVID-19 (Table 3).

Table 3. Association between the Ala222Val polymorphism in the MTHFR gene in groups of patients with MI without a history of COVID-19 virus infection and those with COVID-19 associated MI.

Alleles and genotypes	Number of examined alleles and genotypes				$\chi2$	p	OR	95%CI
	COVID-19 associated MI		MI without COVID-19					
	n	%	n	%				
Ala	79	74,5	62	75,6	0,0	p = 0,90	0,9	0,48 - 1,84
Val	27	25,5	20	24,4	0,0	p = 0,90	1,1	0,54 - 2,06
Ala/Ala	30	56,6	22	53,7	0,1	p = 0,80	1,1	0,5 - 2,56
Ala/Val	19	35,8	18	43,9	0,6	p = 0,50	0,7	0,31 - 1,64
Val/Val	4	7,5	1	2,4	1,2	p = 0,30	3,3	0,39 - 27,18

5. CONCLUSION

As the assessment of the association between the Ala222Val polymorphism in the MTHFR gene in the study groups shows, the calculated relative risk of developing MI in patients with a history of COVID-19 increased when the Ala/Val , Val/Val genotypes and the Val allele were detected, and the risk of developing MI in patients without COVID -19 in history increased when an unfavorable Val allele and an unfavorable Ala/Val genotype were detected.

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