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ACE I/D POLYMORPHISM IN ASSESSING THE SEVERITY OF COVID-19

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Abstract. The results of the studies showed no significant difference in the incidence of ACE I/D polymorphism in the compared groups. No effect of ACE I/D gene polymorphism on the severity of COVID-19 was found. Further studies are planned in the largest cohort of patients to investigate the impact of ACE I/D polymorphism on the course and outcome of COVID-19.

Keywords: COVID-19, ACE I/D polymorphism, DD genotype, ID genotype, II genotype

Introduction. Both virus-specific factors and host inflammatory responses play an important role in determining the severity of the disease and the clinical outcome of COVID-19. In this regard, the identification of various factors that affect the severity of COVID-19 may be useful in assessing the clinical condition of patients and in predicting the severity of the disease. The genetic polymorphisms differ across ethnic groups and may be one reason for the uneven distribution of COVID-19 morbidity and mortality around the world. Given the role of the ACE gene in the renin-angiotensin system and, consequently, in the pathogenesis of COVID-19, many studies have been carried out to study the polymorphism of the ACE I/D gene [1, 2, 3, 4].

The ACE gene is located on chromosome 17 (locus 17q23.3) and encodes an angiotensin-converting enzyme. In the 16th intron of the ACE gene, an insertion-

deletion (I/D) polymorphism was revealed and, therefore, there are three genotypes in the I/D polymorphism: II, ID, and DD. Conducted studies on the impact of ACE I/D polymorphism on the severity and outcome of COVID-19 in different countries are contradictory. In this regard, the study of the role of ACE I/D polymorphism in susceptibility to infection and the course of the disease in different ethnic groups is relevant, since the genetic variations of the organism differ in different populations.

Aim of the study. To study the influence of ACE I/D polymorphism on the severity of the course of COVID-19.

Materials and methods. We examined 112 patients with COVID-19 aged 19 to 89 years, hospitalized at the clinic of the Research Institute of Virology of the Republican Specialized Scientific and Practical Medical Center for Epidemiology, Microbiology, Infectious and Parasitic Diseases. Patients with moderate course - 56 people and severe/extremely severe course - 56 people. The diagnosis of COVID-19 was confirmed by the detection of SARS-CoV-2 RNA in nasopharyngeal swabs by polymerase chain reaction (PCR) during hospitalization of patients. Whole blood was the material for the study of ACE I/D gene polymorphism. Extraction of DNA from clinical material was performed using the DNA-sorb-B kit (Russia). Determination of polymorphism of the ACE I/D gene was carried out by PCR with electrophoretic detection of amplification products in agarose gel using the AmpliSense ACE-I/D-Eph kit (Russia) according to the manufacturer's instructions. Statistical data processing was carried out using Student's t-test and Chi-square test.

Results and discussion. The frequency of occurrence of ACE I/D gene polymorphism was studied in a cohort of COVID-19 patients with moderate and severe/extremely severe disease. The age of patients with a moderate course of COVID-19 was significantly younger and amounted to 51.8±2.1 years (p=0.0002), with severe/extremely severe course – 62.3±1.8 years.

An analysis of the frequency of occurrence of ACE I/D genotypes in the moderate group of patients showed the detection of the DD genotype in 21.4% of

cases, the ID genotype in 44.6%, and the II genotype in 33.9%. The distribution of genotypes in the severe/extremely severe group showed the occurrence of the DD genotype - 23.2% of cases, the ID genotype - 48.2%, and the II genotype - 28.6%. However, ID genotype ($p<0.05$) prevailed over other genotypes in both groups.

Analysis of the distribution of the D allele and I allele of ACE in the moderate group of patients was 56.3% and 43.7% of cases, respectively. Similarly, in the severe/extremely severe group of patients, the D allele occurred in 58.4% of cases, the I allele in 41.6%.

Considering the role of the ACE gene in the renin-angiotensin system and, therefore, in the pathogenesis of COVID-19, we analyzed the frequency of occurrence of ACE I/D gene polymorphism among patients with hypertension. Among all 112 examined patients with COVID-19, hypertension occurred in 63.4% of cases. In patients with hypertension, the DD genotype was detected in 23.9%, ID and II genotypes were more common and were detected in 42.3% and 33.8% of cases, respectively. Among patients with COVID-19 without hypertension, ID genotype was more often detected - 53.7%, while genotype II was found in 26.8%, DD genotype - 19.5% of cases. There was no significant difference in the distribution of genotypes in the compared groups of patients with and without hypertension.

Much attention is paid to the influence of genes on susceptibility to COVID-19 and/or severity. Hundreds of SNPs show significant differences in allele and genotype frequencies between ethnic groups [5]. Data on the frequency of ACE genotypes are contradictory. Research by Bellone M. and Calvisi S.L. [6] and Yamamoto N. et al. [7] identified the D allele as a predictive marker for increased severity of COVID-19. Severe COVID-19 was associated with ACE D/D genotype in a Spanish cohort of patients, where ACE DD genotype was statistically higher in the severe disease group than in the mild disease group (46% versus 32%, respectively). However, in the analysis of risk factors, the ACE DD genotype was not a risk factor for severe disease [8]. A meta-analysis including studies published in 26 Asian

countries found a significant positive correlation between ACE D allele frequency, as well as COVID-19 infection and mortality rates (r-values: 0.52 and 0.620, respectively) [9].

In contrast, studies performed by Delange J.R. et al identified the I/I genotype as detrimental [10]. In contrast, in a study by Ozgur Gunal et al. found that the ACE II genotype was the dominant genotype (50%) in asymptomatic patients, while the ACE DD genotype was the dominant genotype (63.3%) among severe patients. The ACE II genotype was a protective factor against severe disease (OR and 95% CI: 0.323 and 0.112-0.929) [11]. Saadat M. indicates that there is no association between ACE I/D polymorphism and COVID-19 infection [12]. According to this author, in addition to hereditary factors that can affect the prevalence, mortality and mortality from the disease, the economic situation and the level of medical services in different countries should be taken into account. Factors such as country income and the number of diagnostic tests performed show significant differences between countries and can act as confounders when studying the relationship between D allele frequency and prevalence or mortality from COVID-19, and the author believes that these important variables should be included in statistical model in the analysis of research results.

Dhumad M.M., et al. believe that the conflicting results of studies on ACE I/D polymorphism are due to differences in ethnicity, population heterogeneity, sampling bias, biological factors, study design, data analysis, timing of analysis (first or second wave of pandemic), as well as various environmental and social factors that may be associated with changes in the epigenetic state [13].

Our preliminary results showed no significant difference in the frequency of alleles and genotypes of ACE I/D polymorphism in the compared groups of moderate and severe/extremely severe patients.

Conclusions. The frequency of occurrence of ACE I/D gene polymorphisms in the compared groups did not differ and their effect on the severity of COVID-19 was

not found. To study the impact of ACE I/D polymorphism on the course and outcome of COVID-19, further studies are planned in the largest cohort of patients.

References

1. Naser Hatami., Salma Ahi., Alireza Sadeghinikoo., Mahdi Foroughian. et al. Worldwide ACE (I/D) polymorphism may affect COVID-19 recovery rate: an ecological meta-regression. Endocrine. – 2020. Vol.68. P.479-484.

2. Rangaprasad Sarangarajan., Robert Winn., Michael A. Kiebish., Chas Bountra. et al. Ethnic Prevalence of Angiotensin-Converting Enzyme Deletion (D) Polymorphism and COVID-19 Risk: Rationale for Use of Angiotensin-Converting Enzyme Inhibitors/Angiotensin Receptor Blockers. Journal of Racial and Ethnic Health Disparities. – 2021. Vol.8. P.973-980.

3. Noel Pabalan., Phuntila Tharabenjasin., Panan Suntornsaratoon., Hamdi Jarjanazi., Chatchai Muanprasa. Ethnic and age-specific acute lung injury/acute respiratory distress syndrome risk associated with angiotensin-converting enzyme insertion/deletion polymorphisms, implications for COVID-19: A meta-analysis. Infection, Genetics and Evolution. – 2021. https://doi.org/10.1016/j.meegid.2020.104682.

4. Halim Saad., Karna Jabotian., Carine Sakr., Rami Mahfouz., Imad Bou Akl., Nathalie K. Zgheib. The Role of Angiotensin Converting Enzyme 1 Insertion/Deletion Genetic Polymorphism in the Risk and Severity of COVID-19 Infection. Frontiers in Medicine. – 2021. https://doi: 10.3389/fmed.2021.798571.

5. Huang T., Shu Y., Cai Y.D: Genetic differences among ethnic groups. BMC Genomics. - 2015. https://doi.org/10.1186/s12864-015-2328-0.

6. Bellone M., Calvisi SL: ACE polymorphism and COVID-19-related mortality in Europe. Mol Med (Berl). - 2020. – Vol.98. – P.1505-1509

7. Yamamoto N., Ariumi Y., Nishida N., Yamamoto R. И др. SARS-CoV-2 infections and COVID-19 mortalities strongly correlate with ACE1 I/D genotype. Gene. - 2020. https://doi.org/10.1016/j.gene.2020.144944.

8. Gómez J., Albaiceta G.M., García-Clemente M., López-Larrea C. и др. Angiotensinconverting enzymes (ACE, ACE2) gene variants and COVID-19 outcome. Gene. -2020. https://doi.org/10.1016/j.gene.2020.145102.

9. Pati A., Mahto H., Padhi S., Panda A.K. ACE deletion allele is associated with susceptibility to SARS-CoV-2 infection and mortality rate: An epidemiological study in the Asian population. Clin Chim Acta. 2020. – Vol.510. – P.455-458.

10. Delanghe J.R, Speeckaert M.M., De Buyzere M.L: COVID-19 infections are also affected by human ACE1 D/I polymorphism. Clin Chem Lab Med. - 2020. – Vol.58. – P.1125-1126.

11. Ozgur Gunal, Ozlem Sezer, Goksenın Unluguzel Ustun, Cagatay Erman Ozturk. et al. Angiotensin-converting enzyme-1 gene insertion/deletion polymorphism may be associated with COVID-19 clinical severity: a prospective cohort study. Ann Saudi Med. – 2021. – Vol.41(3). – P.141-146.

12. Saadat M. No significant correlation between ACE Ins/Del genetic polymorphism and COVID-19 infection. Clin Chem Lab Med. - 2020. - Vol.58. – P.1127-1128.

13. Dhumad M.M, Hamdan F.B, Al-Mayah Q.S. Angiotensin-converting enzyme insertion/deletion (I/D) gene polymorphism in Iraqi type 2 diabetic patients: association with the risk of cardiac autonomic neuropathy. Egypt J Med Hum Genet. – 2020. – Vol.21. - P.1–7.