Prognostic Significance of Thrombophilia Gene Polymorphism in Covid-19

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ABSTRACT

In the last 20 years, viral infectious diseases have become the most urgent problem in medicine. Severe acute respiratory syndrome (SARS-nCoV) in 2002, Ebola disease in Africa in 2014, Middle East coronavirus syndrome (MERS-CoV) in 2015, and Zika fever in 2016 can be examples [3]. The coronavirus infection caused by SARS-CoV-2 caused a pandemic, unlike previous diseases, and once again proved the need for in-depth study of these diseases.

Keywords:

In the last 20 years, viral infectious diseases have become the most urgent problem in medicine. Severe acute respiratory syndrome (SARS-nCoV) in 2002, Ebola disease in Africa in 2014, Middle East coronavirus syndrome (MERS-CoV) in 2015, and Zika fever in 2016 can be examples [3]. The coronavirus infection caused by SARS-CoV-2 caused a pandemic, unlike previous diseases, and once again proved the need for in-depth study of these diseases.

According to the modern interpretation, thrombophilia is a blood pathological condition characterized by temporary or permanent thrombogenic risk and the development of thrombosis [24, 25]. Thrombogenic risk factors are genetic and transitory, and are complicated by thromboses if not treated in time. Currently, more than 100 secondary thrombogenic risk factors have been identified [32].

Thrombophilia genes include the methylenetetrahydrofolatereductase (MTHFR), methionine synthase (MTR), and methionine synthase reductase (MTRR) genes. These genes are involved in the metabolism of folic acid, ensuring the conversion of homocysteine into the amino acid methionine. The polymorphism identified in the MTHFR, MTR and MTRR genes causes an increase in blood homocysteine and hypercoagulation [5, 6, 12, 29, 41].

Homocysteine damages the endothelial layer of blood vessels and activates the coagulation process [30]. As a result of increased oxidant stress and endothelial dysfunction due to increased homocysteine, the amount of thromboxane A2 increases and platelet aggregation increases [22].

According to the literature, homocysteine disrupts the activity of tissue plasminogen activator, causes the aggregation of lipoprotein and fibrin, as a result of which fibrinolysis decreases. At the same time, homocysteine in high concentration disrupts the activity of antithrombin III and protein, which are natural anticoagulants, changes the normal antithrombotic properties of the endothelium, which activates blood clotting factors V, X and XII [7, 18, 19].

Studies have shown that as a result of genetic changes, the risk of cardiovascular diseases increases several times, heart attacks and strokes are more common in these patients

compared to people without genetic predisposition [4, 11, 26, 27, 36]. At the same time, polymorphism of thrombophilia genes is the main cause of ischemic stroke in children [23, 34, 35, 40]. The S677T polymorphism in the MTHFR gene, which leads to the exchange of cytosine to thymine in diabetes, causes many complications in a short time, including the progression of diabetic nephropathy [31].

The study of the association of thrombophilia genes, which increase the risk of thrombosis, showed that in the genotype of patients with chronic obstructive pulmonary disease, the condition of thrombophilia is often observed when heterozygous polymorphisms of F2 20210 G/A gene, F5 Arg506Glu gene, and MTHFR 1298 A>C gene are found [1].

The results of the study showed that severe coronavirus infection is mainly observed in elderly patients, and these patients have a high risk of developing thromboembolic complications. Thromboembolic complications are mainly observed in the blood vessels of the heart and brain [2, 8].

As a result of endothelial cell alteration and cytokine storm induced by SARS-CoV-2, the causative agent of COVID-19, hypercoagulopathy occurs during the course of the disease. Unfortunately, as a result of this, in patients with COVID-19, as a result of thromboses in vital organs, disability and death are observed [13, 14, 15]. Therefore, the study of the MTHFR gene A1298C (rs 1801131), C677T (rs 1801133) polymorphisms in the Uzbek population and the significance of the C (rs 1801131) and T (rs 1801133) minor alleles of this gene in the pathogenesis of COVID-19 and in patients with hyperhomocysteinemia It is important to assess the extent of the disease of COVID-19 [9, 16, 21]. By identifying this, it is possible to prevent various severe complications that can be caused by COVID-19 by selecting those who have a tendency to develop the disease in a severe form, and by conducting special prophylactic and therapeutic procedures [10, 33, 38, 39].

Taking into account the importance and relevance of thrombophilia, the application of modern molecular diagnostics of thrombophilia genetic risk factors to various fields of clinical medicine is very important for the prevention of many complications caused by thrombosis. [28, 37].

One of the main causes of death in coronavirus infection is the development of hypercoagulation, the development of thrombophilia and the increased risk of thrombosis [17, 20]. At the same time, in medicine, a gene polymorphism that causes a tendency to thrombophilia and a high risk of developing thrombosis has been identified, and the state of hemostasis in patients with COVID-19 with this genetic polymorphism has not been studied [].

The purpose of the study: to determine the polymorphism of thrombophilia genes in patients with coronavirus infection and to determine their correlation with changes in the hemostasis system.

Material and methods. In clinical studies, 60 patients with coronavirus infection, who were healthy from a young age and did not have comorbidities, who were treated in 2021 at the Zangiota Infectious Diseases Hospital, were examined. Self-diagnosis. Version 10 of SSV "Provisional recommendations for treatment of patients with coronavirus infection" was used.

The age of the patients in the study ranged from 18 to 40 years, with a mean age of 28.9 ± 7.6 years. 28 (56%) of the patients were women, 22 (44%) were men.

Group 1 was divided into 15 (25%) patients with mild coronavirus infection, group 2 was divided into 20 (33%) patients with moderate coronavirus infection, and group 3 was divided into 25 (42%) patients with severe and severe coronavirus infection. established by the patient. The control group consisted of 15 healthy people with a negative polymerase chain reaction test for coronavirus infection.

Polymorphism of MTHFR 1298, MTHFR 677, MTRR 66 and MTR 2756 genes in venous blood of patients was studied using polymerase chain reaction. Polymerase chain reaction was carried out on a DT-Lite 48 amplifier using DNA-technology (Russia) reagents.

Homocysteine and D dimer were determined in patients' venous blood by

immunoenzyme method, using Human (Germany) reagents, MR-96A Mindray (China) immunoenzyme analyzer.

Platelet adhesion was studied by passing 350 µg of blood mixed with sodium citrate at a ratio of 9:1 through a glass fiber. Platelet aggregation was determined by hemolysate aggregation test of 10-2 and 10-6 blood mixed with sodium citrate in a ratio of 9:1.

AQTV and fibrinogen were determined in a 4-channel BioSystems (Spain) COAX semi-automatic coagulometer, using Human (Germany) reagents.

Research results. In a clinical study, thrombophilia genes were examined in the blood of 60 patients with coronavirus infection. Genetic studies of 15 (25%) patients in group 1 showed that no polymorphisms of MTHFR 1298, MTHFR 677, MTRR 66 and MTR 2756 genes were observed in all patients with mild disease. The amount of homocysteine in these patients was 5.2 ± 0.4 µmol/l. In the control group, the amount of homocysteine was 4.8 ± 0.7 µmol/l.

Analysis of the results of 20 (33%) patients with moderate-severe disease in group 2 showed that 2 patients had heterozygous polymorphism in MTHFR 1298 gene, 1 patient had heterozygous polymorphism in MTHFR 677 gene, and 2 patients had heterozygous polymorphism in MTRR 66 and MTR 2756 genes. Examination of the level of homocysteine in these patients showed that the level did not exceed the normal level in patients without thrombophilia gene mutation, while the level of homocysteine was reliably high in patients with gene polymorphism. The amount of homocysteine in patients without genetic polymorphism was 5.6 ± 0.5 µmol/l, in patients with MTHFR 1298 gene polymorphism it was 18.7 ± 1.9 µmol/l***, in patients with MTHFR 677 gene polymorphism it was 19.9 ± 2.1 µmol /l*** was 15.8 ± 1.4*** and 14.7 ± 1.2*** µmol/l in polymorphism of MTRR 66 and MTR 2756 genes, respectively (Fig. 1).

Heterozygous polymorphism was observed in 11 patients of group 3. In particular, heterozygous polymorphism on 1 gene was detected in 7 patients: MTHFR 1298 gene polymorphism in 2 patients, MTHFR 677 gene polymorphism in 3 patients, MTRR 66 gene polymorphism in 1 patient, MTR 2756 gene polymorphism in 1 patient. Polymorphism on 2 genes was detected in 4 patients: polymorphism of MTHFR 1298 and MTRR 66 genes was observed in 2 patients, polymorphism of MTHFR 677 and MTR 2756 genes was observed in 1 patient, polymorphism of MTHFR 677 and MTRR 66 genes was observed in 1 patient.

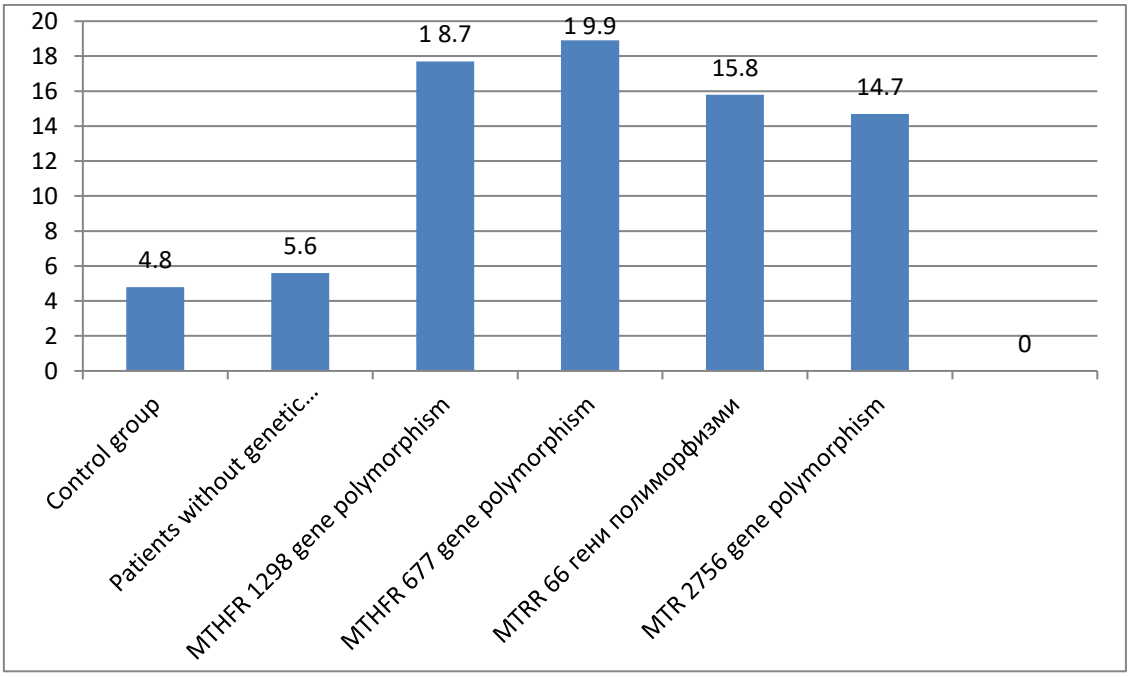

Figure 1. Amount of homocysteine in group 2 patients, µmol/l.

Determination of homocysteine in this group of patients showed that there is a correct correlation between the amount of homocysteine, the number and type of polymorphism in genes: it was found that the amount of homocysteine was higher in patients with 2 gene polymorphisms compared to 1 gene polymorphism (Fig. 2).

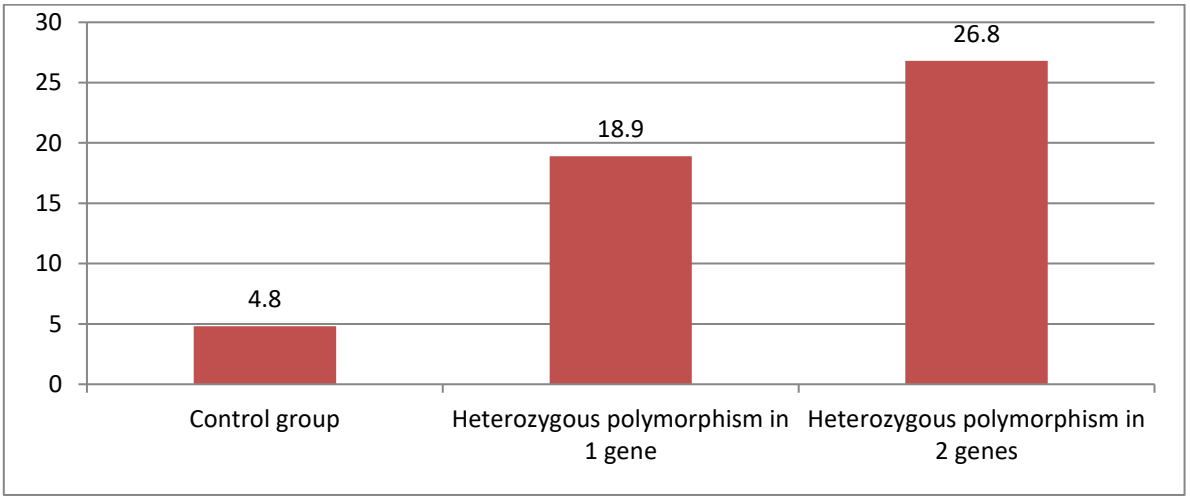

Figure 2. Amount of homocysteine in patients of 3 groups, µmol/l.

As can be seen from the table, the amount of homocysteine in patients with polymorphism in 1 gene was 18.9 ± 1.4 µmol/l ***, and in patients with polymorphism in 2 genes, the amount of homocysteine was 26.8 ± 1.9 µmol/l ***.

In order to study the status of all stages of hemostasis in the patients selected in the clinical study, platelet count, platelet adhesion and aggregation activity, active partial thromboplastin time (AQTV), fibrinogen and D-dimer levels were studied.

The study of platelet count showed that polymorphism of thrombophilia genes did not cause a reliable change in platelet count. It was found that the amount of platelets in group 1 was 248 ± 30 x109/l, in group 2 the number of platelets was 286 ± 35 x109/l, in patients with heterozygous polymorphism it was 305 ± 40 x109/l, in group 3 it was 274 ± 33 x 109/l in patients with polymorphism. . The number of platelets in the control group was 256 ± 39 x 109/l.

The study of platelet adhesion showed that platelet adhesion activity increased in all groups, and this indicator was significantly higher in groups with thrombophilia gene polymorphism. In group 1, platelet adhesion was 37 ± 4.9%, in group 2, platelet adhesion was 50 ± 4.7%*** in patients without thrombophilia gene polymorphism, in patients with heterozygous polymorphism, platelet adhesion was 61.3 ± 5.2%***, 3 It was observed that platelet adhesion was 62.2 ± 5.6%*** in patients with heterozygous polymorphism in 1 gene, and 69.8 ± 6.1%*** in patients with heterozygous polymorphism in 2 genes. In the control group, this indicator was 30 ± 2.9%.

The analysis of platelet adhesion activity showed that the adhesion property increased by 18.9% in group 1 patients with coronavirus infection, platelet adhesion increased by 33.3% in patients without thrombophilia gene polymorphism in group 2, and by 71% in patients with heterozygous polymorphism; In 3 groups, platelet adhesion increased by 85% in patients with heterozygous polymorphism in 1 gene, and by 99.3% in patients with heterozygous polymorphism in 2 genes. In conclusion, it can be said that platelet adhesion property increases during coronavirus infection, and this indicator increases sharply when thrombophilia gene polymorphism is detected.

The study of platelet aggregation activity induced by ADF also showed analogous changes. In group 1, platelet aggregation is 14.5 ± 1.1 sec at GAT 10-2 dilution, 29.5 ± 1.8 sec at GAT 10-6 dilution, in group 2, platelet aggregation in patients without thrombophilia gene polymorphism is 12.6 at GAT 10-2 ± 1.3 sec*, 25.5 ± 2.0 sec in GAT 10-6**, platelet aggregation in patients with heterozygous polymorphism 10.1 ± 0.9 sec in GAT 10-2***, GAT 10-6 20.4 ± 2.2 sec*** in 3 groups, 9.9 ± 0.8 sec*** in GAT 10-2, 19.1 ± 1 in GAT 10-6 in patients with heterozygous polymorphism in 1 gene, 6 sec***, when heterozygous polymorphism was detected in 2 genes, it was observed to be 8.3 ± 0.7 sec*** in GAT 10-2, 17.2 ± 1.5 sec*** in GAT 10-6. In the control group, platelet aggregation was 16 ± 0.9 seconds in GAT 10-2 and 33 ± 1.1 seconds in GAT 10-6.

According to the results of the analysis of platelet aggregation activity, platelet aggregation is 11-15% in group 1, platelet aggregation is 20-22% in patients with no change in thrombophilia genes in group 2, 33-39% when polymorphism of thrombophilia genes is detected, group 3 is in patients with heterozygous polymorphism in 1 gene. platelet aggregation was observed to increase by 45-46%, when heterozygous polymorphism in 2 genes was detected by 52-53%.

As a result of the study of AQTV representing the 1st stage of coagulation hemostasis, it was found that this indicator was reduced in all groups. AQTV in group 1 was 27.5 ± 1.3 sec., in group 2 patients without thrombophilia gene mutations were 22.4 ± 1.5 sec*, when heterozygous polymorphism was detected 20.1 ± 1.6 sec**, group 3 was heterozygous in 1 gene 19.6 ± 1.5 sec** in patients with polymorphism, 17.8 ± 1.4 sec*** when heterozygous polymorphism in 2 genes was detected. In the control group, this indicator was 30 ± 2.8 seconds.

In the analysis of AQTV, it was found that AQTV increased by 6% in group 1, platelet aggregation increased by 10.4% in patients without polymorphism of thrombophilia genes in group 2, by 19.3% when polymorphism was detected, and by 21.6% in patients with polymorphism in 1 gene in group 3 , 43.2% reduction was observed when polymorphism was detected in 2 genes. This indicates hypercoagulable changes.

The amount of fibrinogen, which is the 1st factor of blood coagulation, is high in coronavirus infection, and when the polymorphism of thrombophilia genes is detected, the indicator increases sharply. The amount of fibrinogen in group 1 was 4.55 ± 0.32 g/l*, in group 2 it was 4.88 ± 0.38 g/l** in patients without thrombophilia gene pathology, and 5.33 ± 0.4 g when thrombophilia gene heterozygous polymorphism was detected /l***, 5.98 ± 0.5 g/l*** in patients with heterozygous polymorphism in 1 gene in 3 groups, 6.42 ± 0.5 g/l*** in patients with heterozygous polymorphism in 2 genes . In the control group, this indicator was 3.53 ± 0.2 g/l.

Analysis of fibrinogen changes showed that fibrinogen was 13.7% in group 1, 22.0% in patients without thrombophilia gene polymorphism in group 2, 33.3% in patients with heterozygous polymorphism in group 3, 49.5% in patients with heterozygous polymorphism in 1 gene in group 3. An increase of 60.5% was observed when heterozygous polymorphism was detected in 2 genes.

D-dimer, a product of thrombus breakdown, was observed to be dramatically increased in patients with coronavirus infection and thrombophilia gene polymorphism. The amount of D dimer in group 1 was 180 ± 22 ng/ml, in group 2 patients without thrombophilia genes polymorphism was 260 ± 28 ng/ml**, when heterozygous polymorphism was detected 320 ± 31 ng/ml***, in group 3 heterozygous polymorphism was detected in 1 gene 350 ± 33 ng/ml*** in patients, 480 ± 38 ng/ml*** when heterozygous polymorphism in 2 genes was detected. In the control group, this indicator was 154 ± 12 ng/ml.

The study of the amount of D dimer showed that in group 1, when the amount of D dimer is normal, in group 2, it is 2.3% in patients without thrombophilia gene polymorphism, when heterozygous

polymorphism of thrombophilia genes is detected, by 31.7%, when heterozygous polymorphism in 1 gene is detected in group 3, 44, increased by 0%. When heterozygous polymorphism was detected in 2 genes in 3 groups, it was observed that D dimer increased almost 2 times.

Summary. 1. Polymorphism of thrombophilia genes was not observed in group 1, heterozygous polymorphism of thrombophilia genes was detected in 5 patients in group 2, and in 11 patients in group 3. Homocysteine levels were found to be high in patients with thrombophilia gene polymorphisms.

2. The polymorphism of thrombophilia genes did not cause a reliable change in the amount of platelets, but it was observed that platelet adhesion activity during coronavirus infection increased by 18.9-33.3% in patients without thrombophilia gene polymorphism, and by 85-99% when heterozygous polymorphism was detected.

3. Platelet aggregation was observed to increase by 20-22% in patients without thrombophilia genes, and by 45-53% when heterozygous polymorphism was detected.

4. AQTV thrombophilia genes representing coagulation hemostasis were reduced to 22.4 ± 1.5 sec* in patients without polymorphism, and to 20.1 - 17.8 ± 1.2 sec when heterozygous polymorphism was detected.

5. The amount of fibrinogen increased up to 22.0% in patients without thrombophilia gene pathology, and up to 33.3-60.5% when heterozygous polymorphism was detected. In patients without polymorphism of D-dimer thrombophilia genes, it was observed to increase up to 2.3%, and up to 2 times when heterozygous polymorphism was detected.

6. In conclusion, the study of the hemostasis system showed that a strong hypercoagulability condition was detected in the groups where the polymorphism of the thrombophilia genes was determined.

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