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RISK FACTORS FOR THROMBOEMBOLIC COMPLICATIONS IN PATIENTS WITH Ph-NEGATIVE MYELOPROLIFERATIVE DISEASES

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Abstract. In this paper, we studied theая prognostic significance rof the rs1801133 polymorphic locus of the MTHFR gene in the developmentof venous thromboembolic complications in patients with Ph-negative MPD.
The results obtained indicate that there is a tendency to form a hypercoagulable syndrome and the risk of thrombosis in patients with MPD with the presence of the unfavorable 677T allele of the MTHFR gene in the genotype. The results of the study indirectly indicate the regulatory "suppressive" effect of allelic variants 677T of the rs1801133 polymorphism of the MTHFR gene on the production of the MTHFR enzyme, leading to hyperhomocysteinemia, which is an important confirmation of the significance of genetic factors in the body's susceptibility to various thromboembolic complications in MPD.
Key words: Ph-negative myeloproliferative diseases, methylenetetrahydrofolate reductase, hyperhomocysteinemia, thromboembolism.

Relevance of the problem. Chronic Ph-negative миелопролиферативные myeloproliferativeodiseases (MPD) are a group of pathogenetically identical hematological diseases, includingих erythremia, essential thrombocythemia (ET), and ideopathic myelofibrosis (IMF) [3, 6, 13]. These diseasesare caused by chronic leukemias with damage at the level of the hematopoiesis progenitor cell with unlimited proliferation of this cell characteristic of the tumor, the descendants of which are differentiated by all hematopoietic sprouts. (4, 7, 11). Classical chronic MPDs are acquired sporadic disorders of hematopoiesis, but hereditary forms of myeloproliferative diseases are also known-familial erythremia and thrombocythemia. Diagnosis and treatment of chronic MPD is an urgent problem of modern hematology. Until recently, the molecular defects and corresponding markers of IP, ET, and IMF were unknown. Therefore, the arsenal of routine laboratory methods used to diagnose classical Ph-negative chronic MPD was limited to the method of obtaining endogenous erythropoietin-independent colonies (EEC), evaluating clonality, and determining the level of erythropoietin and thrombopoietin in the blood of patients [1, 8, 12]. The recently increased interest in this disease is due to a significant increase in the frequency of diagnosis of chronic MPD in patients of different ages, as well as a high risk of developing thromboembolic complications in this category of patients, which are the main cause of adverse outcomes and mortality (2, 10).
Methylenetetrahydrofolate reductase (MTHFR) isaurinary regulator of homocysteine metabolism in the blood. Carriage of an unfavorable genotypic variant of polymorphism C677T (rs1801133) of the MTHFR gene, which synthesizes a protein with reduced activity and increased thermal stability, is associated with the development of hyperhomocysteinemiain plasma, which is an independent risk factor for the development of various thromboembolic complications. Hypercoagulable condition in the form ofvenous thrombosis is one of the most serious complications in patients with Ph-negative MPD.
Despite intensive research, data on the role локуса C677of the C677t locus of the MTHFR gene in the formation of individual predisposition to certain thrombotic complications among patients with Ph-negative MPD remain very contradictory. This was the basis for conducting this study. Patients with MPH have a high risk of thrombotic complications, disease progression with transformation into secondary acute myeloid leukemia, and blast crisis [5, 9]. Due to the

importance of molecular markers for both diagnosis and assessment of the risk of complications and the risk of disease progression, this study will allow us to assess the role C677of the C 677t polymorphism of the MTHFR gene in the development of thromboembolic complications in patients with Ph-negative myeloproliferative diseases.

Goals and objectives of the study. To assess the prognostic significance of polymorphic locus rs1801133 of the MTHFR gene with the development of venous thromboembolic complications in patients with Ph-negative MPD.

Materials and methods. The study included DNA samples from 69 patients with MPD (39-erythremia, 17-essential thrombocythemia, 13-subleukemic myelosis). Among these patients, 30 had various forms of thromboembolic complications. Genomic DNA extraction from peripheral blood cells was performed using the Ampli PrimeRIBOT Prep kit. Detection of the rs1801133 locus of the MTHFR gene was performed by allele-specific PCR on a thermocycler Applied Biosistems-2720 (USA), using kits of Litech LLC (Moscow), according to the manufacturer's instructions.

Statistical processing of the results (case-control design) was performed using the OpenEpi statistical software package (ver. 9. 3).

The results obtained and their discussion.

In the main and control groups, the level of observed heterozygosity did not exceed the theoretically expected values, and the rs 1801133 locus1801133 of the MTHFR gene was in accordance with the Hardy-Weinberg equilibrium ($p>0.05$).

In the studied groups of patients with MPD with and without thromboembolic complications, the 677C allele prevailed in frequencyC, occurring in 66.8% (41/60) and 75.4% (63/78), respectively. In the subgroup of patients with thrombosis, there was a tendency to increase the frequency of the 677T a allele associated with reduced MTHFR по cpactivity in comparison with patients without thrombosis (31.7% vs. 19.2%, respectively). The calculated relative chance of detecting this allele in patients with thrombosis compared to the subgroup without thrombosis was OR=1.9 (χ^2=2.8; p=0.09). The relative for the formation of hypercoagulation syndrome and the development of thrombosis was RR= 1.6.

The frequency of occurrence of C/C, C/T, and T/T genotypes in the studied subgroup of patients with and without thrombosis was 43.3%, 50.0%, and 6.7% versus 64.1%, 31.3%, and 2.6%, respectively. The wild C/C genotype was associated with a protective effect on the body's susceptibility to hypercoagulable syndrome (43.3% and 64.1%, respectively; χ^2=3.0; p=0.09; OR=0.4). The heterozygous S/T genotype was recorded significantly more often (a tendency to a significant difference) in patients with thrombosis, than in the control group (50.0% vs. 31.3%, respectively). According to the calculated odds ratio, the carrier of this genotype tended to increase the riska pof developing thrombosis by 2.0 times (χ^2=1.9; p=0.2,; OR=2;), which confirms the version about the involvement of this marker in the development of various thrombotic complications in this pathology.

The homozygous T/T genotype was found only in 2 patients (6.7%) with thrombosis and in 1 without thrombosis (6.7% vs. 2.6%, with p>0.05). The odds ratio was OR=2.6, the relative risk of thrombosis was RR=2.6.

The data obtained indicate that the presence of the rs 1801133 polymorphiclocus1801133 of the MTHFR gene is an independent factor that increases the risk of thrombotic complications. The occurrence of thrombotic complications is a criterion for the unfavorable development of chronic MPD and can be consider as a factor in the negative prognosis of the disease. Along with the leading factors that increase the risk of thrombosis (age over 60 years and a history of cardiovascular risk factors), mutational status can also affect the course of MPD. Thus, the carrier

of a mutation of the rs1801133 polymorphic locus of the MTHFR gene is associated with a significant increase in the risk and frequency of thrombosis in this pathology.
Thus, the method developed by us for quantitative determination of the rs1801133 polymorphic locus of the MTHFR gene by PCR highly specific, sensitive, and can complement morphological, cytogenetic, and other studies. It allows a more adequate assessment of the risk of developing thromboembolic complications, a deep study of the dynamics of minimal residual disease during treatment with various drugs in patients with MPD, allowing not only to diagnose, but also to quantify the effectiveness of specific therapy.

The data available in the literature on the role of these individual genetic markers are few and contradictory. Only a detailed study of the population features of the above-mentioned genetic mutations and an assessment of the correlation between the genotype and phenotype of the disease can make it possible to choose the right strategy for early diagnosis and prognosis, as well as the development of preventive measures for thromboembolic complications in patients with MPD. The obtained data will improve the assessment of the clinical and prognostic significance of the carriage of molecular genetic rearrangements in MPD and will contribute to updating therapeutic approaches and algorithms, which will optimize the treatment and personalize the tactics of therapy for this disease.

Conclusion. The study showed, that molecular genetic analysis of mutations in the rs1801133 polymorphic locus of the MTHFR gene plays an exceptional role in assessing the risk of thrombotic complications in classic Ph-negative MPD. It can be included in the disease prognosis assessment scale as an independent factor. Additional studies are needed to clarify the role of other molecular events in the formation of the phenotype of each individual nosology in the group of Ph-negative MPD.3The new data are of indisputable importance for the synthesis of targeted drugs. Themolecular pathogenesis of chronic MPD is associated with somatic mutations of regulatory genes. This observation serves as a strong argument in favor of the fact that when further studying the molecular causes of occurrence, development, as well as clinical diversity, risk assessment of thrombotic complications in MPD, special attention should be paid to the significance of the polymorphic locus rs1801133 1801133 of the MTHFR gene.
Thus, the obtained data indicate that there is a tendency to form a hypercoagulable syndrome and the risk of thrombosis in patients with MPD with the presence of the unfavorable 677T allele of the MTHFR gene in the genotype. The results of the study indirectly indicate the regulatory "suppressive" effect of allelic variants 677T of the rs1801133 polymorphism of the MTHFR gene on the production of the MTHFR enzyme, leading to hyperhomocysteinemia, which is an important confirmation of the significance of genetic factors in the susceptibility of the body to various thromboembolic complications in hematological cancer patients.

A timely diagnosis and regular monitoring of treatment using clinical, morphological, cytogenetic and molecular genetic research methods is a prerequisite for correct prediction of the course of the disease and achieving maximum effectiveness of therapy. It seems appropriate to study the impact of genetic rearrangements on the clinical course, possible potentiation of the risks of thromboembolic complications, and overall prognosis of MPD.

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