UDC: 616.151.5-084

THE PROBLEM OF THROMBOPHILIA IN CLINICAL PRACTICE (LITERATURE REVIEW)

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Abstract

The review presents an analysis of domestic and foreign literature on the significance of the most common forms of thrombophilia in the formation of the risk of developing thromboembolic diseases. Modern views on thrombophilia , their significance in the occurrence of arterial and venous thromboses and the authors' opinions on the further development of this issue are presented. The article shows the role of hyperhomocysteinemia , dysfibrinogenemia , antiphospholipid syndrome as a risk factor for the development of thromboembolic complications in cardiovascular diseases.

Keywords: thrombophilia, hemostasis, arterial thrombosis, venous thrombosis, hyperhomocysteinemia , dysfibrinogenemia , antiphospholipid syndrome.

KLINIK AMALIYOTDA TROMBOFILIYA MUAMMOSI (ADABIYOT SHARHI)

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Annotatsiya

Ushbu sharxda tromboembolik kasalliklarning rivojlanish xavfini shakllanishida trombofiliyaning eng ko’p tarqalgan turlarini axamiyati haqida mahalliy va xorijiy adabiyotlarni tahlili qeltirilgan. Trombofiliyalar haqida zamonaviy tushuncha, ularning arterial va venoz trombozlarning yuzaga kelishidagi axamiyati va mualliflarning ushbu masalaning keyingi rivoji haqidagi fikrlari bayon qilingan. Maqolada gipergomotsisteinemiya, disfibrinogenemiya, antifosfolipid sindromining yurak qon-tomir kasalliklarida trombotik asoratlarni rivojlanishida xavf omili sifatidagi o’rni ko’rsatib berilgan.

Kalit so’zlar: trombofiliya, gemostaz, arterial tromboz, venoz tromboz, gipergomotsisteinemiya, disfibrinogenemiya, antifosfolipid sindrom.

ПРОБЛЕМА ТРОМБОФИЛИИ В КЛИНИЧЕСКОЙ ПРАКТИКЕ (ОБЗОР ЛИТЕРАТУРЫ)

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Аннотация

В обзоре представлен анализ отечественной и зарубежной литературы о значении наиболее распространённых форм тромбофилий в формировании риска развития тромбоэмболических заболеваний. Изложены современные взгляды о тромбофилиях, их значении в возникновении артериальных и венозных тромбозов и мнения авторов о дальнейшем развитии данного вопроса. В статье показана роль гипергомоцистеинемии, дисфибриногенемии, антифосфолипидного синдрома как фактора риска развития тромбоэмболических осложнений при сердечно-сосудистых заболеваниях.

Ключевые слова: тромбофилия, гемостаз, артериальный тромбоз, венозный тромбоз, гипергомоцистеинемия, дисфибриногенемия, антифосфолипидный синдром.

Despite the great successes of modern medical science and practice, thromboembolic diseases (TED) still remain an important medical and social problem, being the leading cause of mortality and disability in economically developed countries [6, 10]. According to experts, every tenth inhabitant of the planet experiences such severe consequences of arterial and venous thrombosis during their lifetime as acute myocardial infarction, ischemic stroke, thrombosis of both deep and superficial veins, thrombosis and thromboembolism of the pulmonary artery [11].

The increase in the number of thrombosis and their diagnostics is also observed in other areas of medicine. Therefore, thrombosis is of interest not only to specialists in a narrow field, but are also a general medical problem. Numerous epidemiological studies have established more than one, already traditional, risk factor for thrombosis. Along with them, a significant role in the development of such pathologies is given to the phenomenon of thrombophilia, which is manifested by an increased predisposition of a person to the development of complications such as thrombosis [12, 8].

Thrombophilic state is a set of changes in the hemostasis system that contribute to an increased predisposition to thrombosis in blood vessels of different calibers and locations, as well as organ ischemia due to congenital or acquired disorders in various parts of the hemostasis and hemorheology system . The clinical manifestation of thrombosis is preceded by a condition that is characterized by a high risk of developing sudden pathological thrombus formation [1]. Currently, thrombosis

mortality accounts for about 46% of total mortality, however, in more than half of cases, the cause of their development is thrombophilia [2].

In recent years, increasing efforts of specialists have been drawn to the search for factors that predispose to early, premature occurrence and rapid progression of cardiovascular diseases. Early detection of predictors of development and unfavorable course of the disease allows for proper treatment and prevention of this pathology.

Unlike hemostatic disorders caused by known risk factors for thrombosis, which are transient in nature, thrombophilia is associated with an increased risk of thrombosis throughout the patient's life. Many hereditary and acquired thrombophilic conditions are known, which differ from each other both in the causes of occurrence and in the development of the disease [9].

Timely diagnosis and differentiation of all possible pathogenetic forms of thrombophilia is important for choosing the right treatment tactics and preventing this pathology. In recent years, the causes of development have been studied quite well and precise methods for identifying some thrombophilic conditions have been developed, including recently discovered ones known as hypercoagulation syndrome. At the same time, scientists around the world pay considerable attention to combined thrombophilias , which significantly increase the risk of developing thrombosis and thromboembolic complications in patients [14].

As a result of numerous studies conducted recently, a significant number of primary (genetically determined) and secondary (acquired, symptomatic) thrombophilias have become known , which differ from each other in the causes of occurrence, the nature of the development of disorders in the hemostasis system, complications and prognosis of the disease [15].

Currently, the following types of thrombophilia are distinguished:

1. Hereditary thrombophilia. These include protein C and S deficiencies, resistance to protein C activation, hyperhomocysteinemia, antithrombin III deficiency, and hereditary fibrinolysis defects.

2. Acquired thrombophilia. They occur in chronic infections, malignant neoplasms, cardiovascular failure, allergic and autoimmune pathologies, diabetes mellitus, traumatic injuries, surgical interventions, excess weight, etc.

It should be noted that along with "primitive" thrombophilias , there are a considerable number of forms, mainly acquired, which are characterized by complex disorders in all possible links of the hemostasis system. These pathologies include metabolic (diabetic angiopathies, hyperlipidemic forms, thrombophilia in hyperhomocysteinemia), infectious-immune and autoimmune diseases, including the so-called antiphospholipid syndrome, iatrogenic forms of thrombophilia (in fibrinolytic therapy, heparin thrombocytopenia) [21].

This can be observed in early childhood, as well as in adolescence. In such cases, together with the characteristic clinical picture of thrombosis of veins, arteries and capillaries, instrumental methods of examination (angiography, scintigraphy, thermography, radioisotope and ultrasound diagnostics, etc.) significantly help in establishing a diagnosis. At the same time, assessment of the state of the coagulogram and aggregogram is of great importance for pathogenetic diagnostics, treatment and prevention of thrombosis and thromboembolism, which helps to more correctly determine the functional state of the hemostasis system [24]. Such studies make it possible to promptly detect pathological shifts in the vascular, coagulation, platelet, fibrinolytic and anticoagulant links of the hemostasis system, which are considered important pathogenetic links of thrombogenesis. Laboratory diagnostics of hemostasis system disorders, which was the leading method in identifying the causes of hemorrhagic syndrome, has changed significantly today. These changes primarily affected the establishment of causes of increased thrombus formation, identification of factors of increased risk of tendency to thrombosis development [13].

Congenital deficiency of protein factors C and S is inextricably linked with a predisposition to severe thrombotic disorders. In studies, the most common finding among patients is the Leiden anomaly, which develops as a result of a mutation of factor V (Leiden). These people mainly have hereditary thrombophilia, which is caused by the resistance of factor V to the action of protein C. To detect these mutations, it is necessary to conduct a blood test for polymorphisms. This analysis is currently important for establishing or confirming the diagnosis of thrombophilia. Polymorphisms are mutations that are observed among people more often than 1% of cases. The detection of polymorphism indicates a higher probability of thrombosis, but this is not yet a reason for the inevitability of the obligatory development of thrombotic complications [20].

In recent years, significant advances have been made in the field of human molecular genetics, which have allowed us to move from a formal description of the laws of inheritance to a complete decoding of the human genome. Molecular genetics has created a basis for developing non-standard methods of treatment, disease prevention, and individual, genetically based drug therapy [7].

The current concept of the polygenic nature of hereditary thrombophilia, which notes the presence in most cases of TE of not one, but several genetic variants, independently or synergistically modifying the risk of developing the disease, dictates the need to use significantly different approaches to studying the basis of genetic susceptibility to thrombosis [19]. As a result, considerable attention is paid to the phenomenon of allelic polymorphism, which is characteristic of most human genes, including those whose products participate in the regulation of physiological blood flow. Currently, several dozen genetic varieties are known, the carriage of which is

associated with the development of prothrombotic shifts in the hemostasis system, contributing to the development or risk of developing thromboembolic complications [16].

Dysfibrinogenemia or so-called functional fibrinogen deficiency can also be a cause of predisposition to thrombus formation. Most likely, the prerequisite for the development of thrombophilia is a violation of fibrin-mediated activation of plasminogen, i.e., increased activation by tissue plasminogen-activating factor. In most cases, dysfibrinogenemia is asymptomatic. But very often, cases of hemorrhagic diathesis or thrombophilia are observed. A combination of bleeding and thromboembolism can also be observed. According to estimates by various authors, the reliable prevalence of thrombosis among carriers of dysfibrinogenemia is not exactly known. This complication is diagnosed in 10 to 20% of cases of this pathology [25].

In recent years, hyperhomocysteinemia has been recognized as an independent risk factor for thrombosis [4]. The causes of hyperhomocysteinemia are the sex and age of patients, hereditary factors (folate cycle gene polymorphism), nutritional characteristics (deficiency of folic acid and B vitamins), medication intake, chronic diseases and other factors. The causes of increased homocysteine concentrations (HC) in the blood can be caused by many factors, including defects in the genes of enzymes that control its metabolism. The mechanism of thrombogenic effects of increased homocysteine has not yet been fully studied. A common genetic defect that causes increased homocysteine levels in the blood is a mutation that promotes the formation of a thermolabile variant of M THFR with reduced activity [26].

folate cycle enzyme genes that increase serum homocysteine levels are considered to be very important. These disorders include polymorphisms of the MTHFR 677 C→T, MTR 2756 A→G and MTRR 66 A→G genes, as well as their combinations. Studies have shown that patients with homocysteine levels >15.3 μmol /l, the risk of death from cardiovascular diseases was 1.7 times higher, especially from myocardial infarction - 3.4 times, from stroke - 4.3 times, than in patients with a homocysteine level of no more than 10.5 μmol /l [5].

In recent years, numerous epidemiological and clinical studies have been conducted that have shown that hyperhomocysteinemia increases the risk of early development of atherosclerosis and thrombosis of the coronary, cerebral and peripheral arteries, regardless of traditional risk factors, and such a condition is a prognostic marker of an unfavorable outcome of the disease [3].

Antiphospholipid syndrome (APS) as one of the causes of pathological thrombus formation accounts for 20% to 25% of cases. APS is an autoimmune disease characterized by the formation of autoantibodies to various phospholipids in the cell membranes, mainly platelets, as well as to cardiolipin and β-2-glycoprotein-1

of various classes (IgG , IgM and IgA). In addition, this pathology is characterized by the presence of a coagulological phenomenon - lupus anticoagulant , which ultimately manifests clinically as thrombotic processes with damage to veins and arteries. The term "lupus anticoagulant" refers to a group of immunoglobulins of classes mainly IgG and IgM , which in laboratory conditions inhibit phospholipid-dependent coagulation tests (APTT is prolonged, the prothrombin index may decrease). APS leads to the formation of more frequent thromboses with damage to various calibers of both venous and arterial vessels [23].

Primary APS, secondary APS, catastrophic APS are distinguished. Antiphospholipid syndrome that develops in patients who do not have any other known autoimmune, immune complex or infectious diseases is called primary. It manifests itself as venous or arterial thromboembolism, sterile endocarditis with embolism, recurrent miscarriage.

Secondary APS occurs against the background of other diseases, in particular, autoimmune diseases. Most often, this is systemic lupus erythematosus, less often in lupus-like , undifferentiated and mixed diseases of connective tissue and some other pathological conditions [17]. In recent years, it has become common in the literature to combine primary and secondary APS. APS is characterized by thrombotic lesions of both venous and arterial vessels of small and medium caliber, but sometimes thrombi also occur in large vessels [22].

Catastrophic APS is a very severe pathological condition (among various forms of APS), which is characterized by widespread mixed thromboses in the arterial - venous and also in the arteriolar -capillary bed. This is accompanied by the development of severe multiple organ failure due to damage to many vital organs - the brain, lungs, liver, kidneys, intestines, etc. [18].

The above shows that antithrombotic prophylaxis and therapy are of exceptional importance in this pathology. At the same time, its effectiveness and safety largely depend on modern concepts of the pathogenesis of thrombophilia and thrombosis, as well as knowledge of the pharmacokinetic properties of antithrombotic drugs. Without this, it is impossible to ensure the selection of an appropriate dose of a drug, assess the effectiveness of prophylaxis and treatment, and prevent, in some cases, the most life-threatening hemorrhagic or thrombotic complications of antithrombotic therapy.

It has been established that in the presence of more than one prothrombotic polymorphism, there is a real risk of developing thromboembolic complications. The involvement of thrombophilia in the pathogenesis of various diseases is the basis for its further detailed study and search for the causes of increased thrombus formation in this pathology.

Thus, the practical importance of laboratory methods in this area is difficult to overestimate, as they enable early, preclinical detection of disorders in the blood coagulation system. This makes it possible to predict the development of thrombotic complications, which thereby helps to reduce the incidence of the most common causes of death in this pathology, which are the occurrence of thromboses of various localizations.

References:

1. Vardanyan A. V., Badanyan A. L., Mumladze R. B., Patrushev L. I., Dolidze D. D. Use of DNA diagnostics in treatment tactics of patients with deep vein thrombosis. Annals of Surgery, No. 3, 2014, pp. 12-19.
2. Zhdanova L. V., Patrushev L. I., Dolgikh V. V. Polymorphism of genes responsible for thrombophilia and their influence on the development of thrombosis in childhood. Bulletin of the SB RAMS , 2013, 4(92). Pp. 115-118.
3. Karazhanova L.K., Zhunuspekova A.S. Hyperhomocysteinemia as a risk factor for cardiovascular diseases. Science and Healthcare 4, 2016, pp. 129-144.
4. Kalinin R.E., Suchkov I.A., Rudakova I.N., Nikiforova L.V. Hyperhomocysteinemia and the possibilities of its correction in postthrombotic syndrome of the lower extremities. Bulletin of RUDN, series medicine, 2016, No. 1, pp. 61-66.
5. Levashova O.A., Zolkornyaev I.G. Analysis of homocysteine levels and prevalence of genetic polymorphism of folate cycle genes in patients with ischemic stroke. The Journal of scientific articles “Health and Education Millennium”, 2017. Vol. 19. No. 1, pp. 97-99.
6. Momot A.P. The problem of thrombophilia in clinical practice // Russian Railways, Geophysics, and Orthopedics , 2015, No. 1.
7. Sanets I.A., Silin A.E. , Yarets Yu.I., Anichkin V.V. Genetic markers of venous thromboembolism in surgical patients. News surgery , vol. 26, no. 2, 2018, pp . 155-162.
8. AppelmanY , vanRijnBB , TenHaafME , BoersmaE , PetersSA . Sex differences in cardiovascular risk factors and disease prevention // Atherosclerosis, 2015, Vol. 241, pp. 211-218.
9. Ashraf N, Visweshwar N, Jaglal M, Sokol L, Laber D. Evolving paradigm in thrombophilia screening. Blood Coagul Fibrinolysis. 2019;30(5):249–252. doi:10.1097/MBC.
10. Bounameaux H. ISTH EDUCATIONAL COURSE. Thrombosis and hemorrhage. What are the causes? // Risk factors and pathogenesis of thrombosis. Россия, г. Санкт-Петербург. 2017.

11. Chiasakul T, De Jesus E, Tong J, et al. Inherited Thrombophilia and the Risk of Arterial Ischemic Stroke: A Systematic Review and Meta-Analysis. J Am Heart Assoc. 2019;8(19):e012877. doi:10.1161/JAHA.119.012877.
12. Couturaud F, Leroyer C, Tromeur C et al. Factors that predict thrombosis in relatives of patients with venous thromboembolism. Blood. 2014;124(13):2124–2130.
13. Connors J M. Thrombophilia testing and venous thrombosis. N Engl J Med. 2017;377(12):1177–1187.
14. Garcia-Horton A, Kovacs MJ, Abdulrehman J, Taylor JE, Sharma S, Lazo-Langner A. Impact of thrombophilia screening on venous thromboembolism management practices // Thromb Res, 2017, No. 149, pp. 76-80.
15. Linnemann B, Hart C. Laboratory Diagnostics in Thrombophilia. Hamostaseologie. 2019;39(1):49–61. doi:10.1055/s-0039-1677840.
16. Mahmoodi BK, Cushman M, Anne Næss I, et al. Association of Traditional Cardiovascular Risk Factors With Venous Thromboembolism: An Individual Participant Data Meta-Analysis of Prospective Studies // Circulation, 2017, Vol. 135, No. 1, pp. 7-16.
17. Meroni P.L., Tsokos GC. Editorial: Systemic Lupus Erythematosus and Antiphospholipid Syndrome. Front Immunol. 2019;10:199. Published 2019 Feb 25. doi:10.3389/fimmu.2019.00199.
18. Mezhov V, Segan JD, Tran H, Cicuttini FM. Antiphospholipid syndrome: a clinical review. Med J Aust. 2019;211(4):184–188. doi:10.5694/mja2.50262.
19. Miyata T, Maruyama K, Banno F, Neki R. Thrombophilia in East Asian countries: are there any genetic differences in these countries? Thromb J 2016; 14 Suppl 1:25.
20. Rallidis L, Gialeraki A, Tsirebolos G, Drosatos A, Katsimardos A, Pavlakis G, Iliodromitis E. Factor V Leiden and prothrombin G20210A mutations in patients with premature myocardial infarction // European Heart Journal, 2017, No. 38 (suppl-1), P. 1735.
21. Rosendaal F.R. Causes of venous thrombosis // Thromb J, 2016, No. 14(Suppl 1), P. 24.
22. Shlebak A. Antiphospholipid syndrome presenting as cerebral venous sinus thrombosis: a case series and a review. J Clin Pathol. 2016;69(4):337–343. doi:10.1136/jclinpath-2015-203077.
23. Silver RM. Catastrophic antiphospholipid syndrome and pregnancy. SeminPerinatol. 2018;42(1):26–32. doi:10.1053/j.semperi.2017.11.006

24. Sorigue M, Sarrate E, Morales-Indiano C, Ruiz-Garcia L, Orna E. Applicability of the results of thrombophilia studies in clinical practice. Eur J Intern Med. 2017;39:e27–e28. doi:10.1016/j.ejim.2017.02.022.
25. Stevens SM. Role of thrombophilia testing: con. J Thromb Thrombolysis. 2015;39(3):379–391. doi:10.1007/s11239-015-1170-1.
26. Suchon P, Resseguier N, Ibrahim M, et al. Common Risk Factors Add to Inherited Thrombophilia to Predict Venous Thromboembolism Risk in Families. TH Open. 2019;3(1):e28–e35. Published 2019 Jan 28. doi:10.1055/s-0039-1677807.