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Review

Thrombophilia as a Risk Factor for Thrombosis

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Abstract
The review article presents a contemporary view on the most common causes of hereditary and acquired thrombophilias and their role in the development of venous and arterial thromboses. The examination of patients in accordance with modern requirements consists in determining the causes and risk factors for blood clot formation, as well as implementing secondary prevention of recurrent thrombosis. Analysis of genetic and acquired hemostatic disorders allows us to identify a group of patients who require long-term anticoagulant therapy and mandatory anticoagulant prophylaxis in cases involving a high risk of thromboembolic complications.

Keywords
thrombophilia; venous thrombosis; arterial thrombosis; anticoagulant therapy

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Introduction

Thrombophilia is a clinical condition characterized by an increased susceptibility of the body to intravascular thrombosis under normal conditions, in the absence of other diseases. It is a disturbance of hemostasis and hemorheology that is characterized by an increased predisposition to develop thrombosis or intravascular coagulation, which are based on various acquired and genetically determined hemorheological disturbances [3, 5, 13]

The problem of combating thrombosis is the most relevant for the modern man. About 25 million people worldwide die from blood vessel thrombosis every year. More than 18 million people with arterial thrombosis, the main manifestations of which are myocardial infarction and ischemic stroke, and 7 million people with pulmonary embolism (PE) die. According to the data of Mayo Clinic for the past 25 years, there was no reduction in the frequency of PE and venous thrombosis (VT) in men; however, the frequency of these diseases in women even increased [1].

In autopsy, PE is detected in 7 to 16% of cases. In multi-speciality hospital, PE is observed in 15-20 patients per 1, 000 treated patients, and in 3-5 of cases, it is the cause of death [4, 6].

The frequency of venous thromboembolism (VTE) during pregnancy is 0.13-0.5 cases per 1, 000 pregnant women and 0.61-1.5 cases per 1, 000 female patients in the postnatal period. In approximately 16% of cases, untreated lower extremity deep venous thrombosis (DVT) during pregnancy turns into PE, which, in 43-60% of cases, develops in women on the 4^{th} and 6^{th} weeks of the postnatal period. The maternal mortality rate during childbirth is 2-5 cases per 1, 000 births.

At the same time, the true prevalence of PE and VTE is difficult to determine, since their clinical symptoms are non-specific, and their signs are often subtle [9]. A particular danger of intravascular blood clot formation is its sudden onset. About 50% of patients with massive PE die within 30 minutes after the onset of symptoms. Mortality rate among patients with PE, who did not receive any

treatment, is 30-40%. More than 90% of deaths occur in patients with undiagnosed VTE. In case of timely diagnosis and adequate therapy, this indicator decreases to 8-10% [1, 9].

1. Discussion

In VTE, damage to the vascular wall plays a lesser role as in the formation of arterial thrombosis, since the venous system remains intact. Therefore, the increased tendency of blood to form clots is called thrombophilia [7, 15].

The confirmation of thrombophilia existence was obtained in the mid 70's of the 20th century, when, in 1965, the Norwegian scientist Olav Egeberg described the first family with sharp decrease in antithrombin III (ATIII). The prevalence of AT deficiency in the general population is 1.0 per 5, 000 population. More than 130 different genetic mutations are currently described. Among patients with thromboembolic complications, the incidence of ATIII deficiency is 3 - 8%. Inheritance of ATIII deficiency is usually autosomal dominant. Most carriers of this disease are heterozygotes, since homozygotes die very early due to thromboembolic complications.

In 15 years, the American researcher Dr. Johnny Griffin discovered the second possible cause of thrombophilia, namely deficiency of a natural anticoagulant - protein C. Protein C deficiency is found in one in 200-500 people. About 160 different types of genetic abnormalities that give rise to protein C deficiency are currently described. Homozygous carriers of protein C deficiency with protein level that is below 1% are not viable and die in utero or immediately after birth.

In 1984, Comp P.C., Esmon C.T. described the genetic predisposition to thrombosis due to a deficiency of protein S, which acts as a cofactor for protein C. Synthesis of this protein depends on the presence of vitamin K. Protein S deficiency occurs in approximately one in 500 people.

In 1993, the Swedish scientist B. Dahlback described familial thrombophilia caused by a lack of response to activated protein C. Since the decoding of the defective molecule of the factor V, which consisted in replacing amino acid arginine with amino acid glutamine at position 506, was carried out in the Dutch city Leiden, the disease is known as Factor V Leiden thrombophilia. Today it is known to be one of the most common forms of thrombophilia. It occurs in 20 - 64% of patients with idiopathic VTE [8].

The next stage in the study of thrombophilia was the discovery of the mutation of the gene that is responsible for prothrombin S molecule formation by Dutch scientists in 1996. Poort S.R. *et al.* found nucleotide replacement of guanine with adenine at nucleotide 20210A of the 11th chromosome in the prothrombin gene. The prevalence of this mutation in the population is 2-3%. In carriers of this defect, the risk of thrombophilia rises by 3-5 times.

The association between the frequency of thrombotic events and the level of homocysteine in the blood was detected. Hyperhomocysteinemia affects both the activation of procoagulants and the inhibition of natural anticoagulants. Its level is influenced by age, gender, diet and depends on renal function, smoking, arterial hypertension, hypercholesterolemia, excessive exercise, alcohol and coffee consumption [11].

The discovery of the predisposition to VTE played a crucial role in the problem of thrombophilia, as it allowed physicians to detect the susceptibility to thrombosis in more than half of people suffering from VTE or chronic obstructive pulmonary disease (COPD).

The progress in understanding the causes of thrombosis in the course of identifying thrombophilia markers is presented in Table 1.

Clinically, thrombophilia is indicated by recurrent thrombosis of various localizations, including the pulmonary artery region, organ infarctions occurring in relatively young patients ($<$ 50 years old), family history [23]. The presence of recurrent thrombotic events allows physicians to suspect thrombophilia and administer additional laboratory and instrumental examinations. The risk of recurrent VT and COPD is presented in Table 2.

In hereditary thrombophilia, there is a genetic defect that causes a predisposition to the development of thrombosis. Such state can last for long

Table 1. Dependence of the frequency of detecting a genetic defect of thrombophilia on the discovery of thrombophilia types in people with VT.

Years of discovery	Thrombophilia	Frequency of thrombophilia in VTE, (%)
1965	AT deficiency	about 5
1981	Protein C deficiency	about 10
1984	Protein S deficiency	about 10-12
1994	Factor V Leiden	about 60
1996	Prothrombin 20210A mutation	about 80

Table 2. Reccurence rate of idiopatic VTE in thrombophilia (according to Wu van der Hogen).

Thrombophilia	Frequency in first VTE	Relative risk of first VTE	Reccurence rate of VTE	Relative risk of VTE
AT deficiency	1-2	17.5	2-5	2.5
Protein C deficiency	2-5	11.5	5-10	2.5
Protein S deficiency	1-3	32.4	5-10	2.5
Heterozygous V Leiden mutation	12-20	4.3	40-50	1.3

time, sometimes a lifetime, without any traumatic manifestations. However, the risk of developing VTE in patient with hereditary thrombophilia significantly increases in direct influence of provocative factors (exercise, traumas, intravenous manipulations, surgical interventions, pregnancy, cancer) [16].

The risk of developing VTE in female patients, who are carriers of thrombophilia, significantly increases when using oral contraceptives (OC). The first case of thrombotic complications on the background of OC usage was registered 2 years after the start of their use in 1961. A more thorough comprehensive study showed that, on the background of thrombophilia, when using OC, the risk of developing VTE increases by 11 times [16]. This is especially evident in carriers of the factor V Leiden mutation (Table 3).

A similar trend is observed in hormone replacement therapy. Thus, the administration of hormone replacement therapy on the background of the factor V Leiden mutation leads to an increase in the risk of VTE to 90-180 per 10, 000 population a year [1, 16].

Manifestations of thrombophilia depend on the patient's age [11]. In children, a deficiency of natural anticoagulants (protein C, protein S, and AT)

Table 3. Risk of developing VTE when using OC.

Thrombophilia	Risk of thrombosis
Without using OC	5-8 per 10,000
Use of OC without mutation	within the first year 30 per 10,000
Factor V Leiden mutation without using OC	57 per 10,000
Factor V Leiden mutation with OC usage	285 per 10,000

develops (Table 4).

In adolescents, the same mutations and combined thrombophilia are present. In adults, mutations of the factor V Leiden, heterozygous prothrombin 20210A forms, etc. are of greatest importance (Table 4).

Homozygous mutations or the combination of two or more heterozygous polymorphisms (multigenic thrombophilia) were found to result in the development of thrombosis at a young age (< 45 years) and they are associated with a tendency to relapse [19].

The results of the studies on molecular genetic mechanisms of thrombus formation and anticoag-

Table 4. Dependence of the risk of VTE on the patient's age and thrombophilia type.

Risk of VTE increases by 3-5 times	Adults FII* (heterozygotes) FVL (heterozygotes) PC (heterozygotes), PS (heterozygotes)
Rsk of VTE increases by 10-20 times	Adolescents FVL (homozygotes), AT (heterozygotes) FVL + FII , FVL + PC PS , AT
Risk of VTE increases by more than 100 times	Newborns PC (homozygotes), PS (homozygotes), AT (homozygotes)

Notes: *PC - protein C deficiency; PS - protein S deficiency; AT - antithrombin III deficiency; FVL - resistance to activated protein C; FII - prothrombin 21210A defect.

ulant system showed that in people with heterozygous factor V Leiden mutation, there is a high risk of recurrent VT of cerebral localization [2, 12]. People with heterozygous factor V Leiden mutation have a 5-7 times higher risk of developing VT. In homozygotes, this risk is 50-100 times higher [12, 14].

Secondary (acquired) thrombophilia develops in various diseases and intake of certain drugs (Table 5).

In the presence of other risk factors for VTE in people, who are carriers of thrombophilia, the risk of developing VTE significantly increases. The occurence of thrombosis in the presence of thrombophilia is presented in Fig. 1.

The risk of arterial thrombosis increases in the presence of hyperhomocysteinemia, protein C deficiency, factor V Leiden, protein S deficiency, elevated levels of factors VIII, IX, XI (Table 6).

According to the EPCOT study, in the presence of thrombophilia, arterial thrombosis occurs more often and at a younger age, than in its absence [20]. The presence of thrombophilia contributes to increased thrombus formation in patients with tumors and atrial arrhythmia [22]. The signs of arterial thrombosis include ischemic stroke and episodes of acute coronary insufficiency in young people, multiple miscarriages and fetal death during the formation of the thrombus in the lumen of the placental vessels [17].

The 10^{th} week and the 3^{rd} trimester of pregnancy are considered as critical periods for manifestation of thrombophilia since the complication such as recurrent miscarriages, stillbirth in the third trimester, placental abruption with massive bleeding, retardation of fetal development may occur [10].

The presence of thrombophilia determines the risk of developing the first episode of VT; however, it is not recognized as a risk factor for its recurrence [18].

The presence of erythrocytosis, hyperthrombocytosis, polycythemia, increased hematocrit, isolated hyperthrombocytosis, changes in erythrocyte size should alert the clinician to the primary cause of thrombus formation.

The analytical criteria for genetic and acquired hemostatic disorders are episodes of thromboembolism at a young age, diagnosed thrombosis of mesenteric vessels and cerebral vessels, signs of purpura in a newborn and in the development of the fetus [21]. This will be the group that requires anticoagulant and anti-aggregate therapy and mandatory long-term anticoagulant prophylaxis.

2. Conclusions

Treatment and prevention in thrombophilia should be based on modern examination methods, since the use of conventional therapeutic methods is often inadequate and leads to a relapse of illness and disability of patients.

Table 5. Causes of secondary (acquired) thrombophilia.

Main etiological groups of acquired thrombophilia	Diseases and conditions resulting in thrombophilia
I. Vascular diseases	1. Arterial atherosclerosis. 2. Diabetic angiopathy. 3. Vasculitis. 4. Vascular prostheses, stents.
II. Disturbances of hemorheology III. Platelet pathology	1. Blood stasis (prolonged immobilization, congestive heart failure). 2. Increased blood viscosity (true polycythemia, Waldenstrom's disease, acute leukemia, sickle cell anemia).
IV. Pathological changes in hemostatic proteins	1. Diabetes mellitus. 2. Hyperlipidemia. 3. Myeloproliferative disorders. 4. Paroxysmal nocturnal hemoglobinuria. 5. Geparin-induced thrombocytopenia.
V. Antiphospholipid syndrome VI. Disseminated intravascular coagulation VII. Inflammatory diseases of the colon	1. Surgical trauma, postoperative condition. 2. Malignant tumors. 3. Pregnancy. 4. Use of oral contraceptives and estrogen. 5. Nephrotic syndrome.

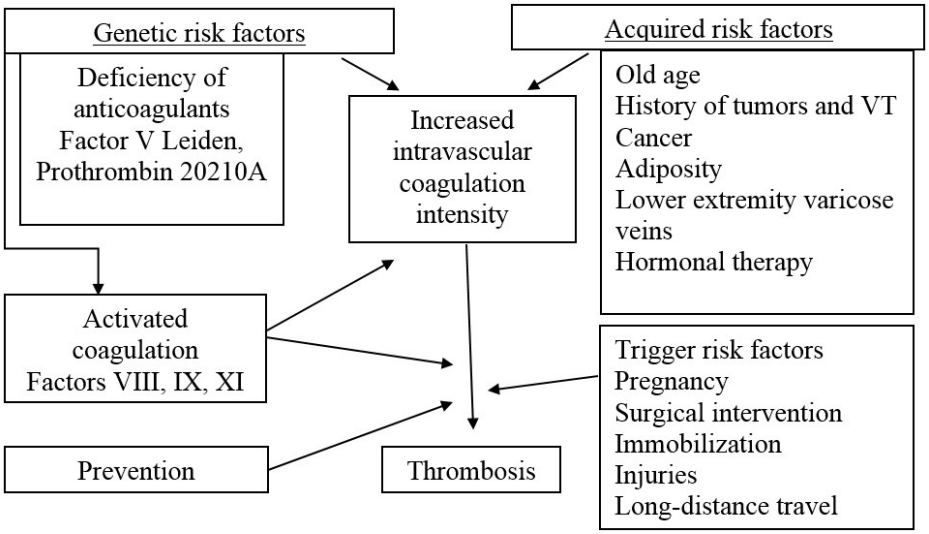

Figure 1. Clinical manifestations of thrombophilia.

Table 6. Atherothrombosis in people with thrombophilia (according to Vossen, 2006).

Causes of thrombophilia	Number of patients	Number of thrombotic events	Myocardial infarction	Stroke	Middle age of manifestation	Number of heart attacks/strokes per 1,000 people a year
Thrombophilia	622	24	15	9	48 (24-67)	1.7 (1.1-2.6)
Protein C deficiency	150	5	-	3	48 (30-65)	1.5 (0.5-3.5)
Protein S deficiency	111	4	3	1	48 (41-58)	1.8 (0.5-4.5)
AT deficiency	92	3	0	3	39 (29-49)	1.5 (0.3-4.3)
Factor V Leiden	208	10	9	1	52 (43-67)	2.1 (1.0-3.9)
More than 1 defect	61	2	1	1	38 (24-53)	1.4 (0.2-5.1)
Control	1125	5	5	0	58 (41-77)	0.2 (0.1-0.4)

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