Characteristics of causes of thrombophilia

Charakterystyka przyczyn trombofilii

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Abstract

Thrombophilia is a clinical condition involving a coagulation system. It is characterized by a hypercoagulation which predisposes to venous thromboembolism and, subsequently, its serious complication: pulmonary embolism. Predominantly, the background of thrombophilia is genetic, concerning mutations of blood coagulation factors. It may also appear in other diseases increasing the risk of thrombosis. The most common type of thrombophilia is the antiphospholipid syndrome. It is crucial to know the risk factors, to diagnose appropriately and possibly early and to prevent thrombosis. A proper treatment significantly reduces the risk of complications.

Key words:

thrombophilia, background, hypercoagulation

Streszczenie

Trombofilia jest stanem klinicznym zaburzającym funkcję układu krzepnięcia. Charakteryzuje się nadkrzepliwością, która predysponuje do wystąpienia żylnej choroby zakrzepowo-zatorowej, a w konsekwencji do poważnego powikłania, jakim jest zator płucny. Najczęstszą przyczyną trombofilii są uwarunkowania genetyczne pod postacią mutacji czynników biorących udział w procesie krzepnięcia krwi. Może pojawić się również w przebiegu innych jednostek chorobowych, zwiększając ryzyko zachorowania na zakrzepicę. Najczęściej występującą trombofilią nabytą jest zespół antyfosfolipidowy. Istotna jest znajomość czynników ryzyka, odpowiednia i wczesna diagnoza oraz profilaktyka przeciwzakrzepowa. Odpowiednie leczenie znacznie zmniejsza ryzyko wystąpienia powikłań.

Słowa kluczowe:

trombofilia, przyczyny, nadkrzepliwość

Introduction

Thrombophilia is a hemostatic system disease which significantly increases the risk of thrombosis, especially venous. In the view of the background of the disorder, we divide thrombophilia into congenital or acquired [1,2].

Congenital thrombophilia

The congenital thrombophilia is associated with inborn genetic mutations which increase the risk of venous or, rarely, arterial thrombosis. In most cases, the mutations spoil products of genes that normally inhibit the coagulation process in the body or, otherwise, stimulate genes that synthesize clotting factors. These pathologies are characterized mainly by an autosomal inheritance with a heterozygous form. Congenital thrombophilia may also be a consequence of multigene abnormalities. Among all people with hemostatic system defects, the most common cause is the mutation of factor V (Leiden) and prothrombin gene polymorphism [2,3].

Acquired thrombophilia

The acquired thrombophilia is a coagulation disorder that occurs in other diseases presenting the risk of thrombosis. Primarily, it is represented by two units: the antiphospholipid syndrome and the condition of elevated homocysteine concentration associated with hypothyroidism or renal failure. This category also includes other immunological disorders, connective tissue diseases, tumors and hypercoagulation due to chemotherapy, as well as some infections and inflammatory diseases such as Crohn's disease [2].

This work summarizes the knowledge concerning the pathogenesis of thrombophilia and sorts out the main reasons of congenital and acquired disorder.

Causes of congenital thrombophilia

Deficiency of Protein C

The Protein C is a two-chain vitamin K-dependent glycoprotein produced in liver cells. It circulates in a blood plasma in the form of serine proteine proenzyme. The zymogenic form of Protein C is bounded to the corresponding receptor located in the vascular endothelium, where it is activated. The process is highly promoted by the thrombin-thrombodulin complex. The main task of an Activated Protein C (APC) is to inhibit Factors Va and VIIIa which is performed through partial proteolysis. The degradation of Factors Va and VIIIa occurs on the surface of phospholipids in the thrombocytes. Protein S acts as a cofactor here. Furthermore, the process is enhanced by a heparin. APC is inactivated by an inhibitor synthesized also in hepatocytes [2,4].

Protein C deficiency is divided into two main types. Type I (quantitative) is much more frequent and it is characterized by a decreased Protein C level. Type II (qualitative), on the other hand, exhibits a normal level of the protein, however, it works inefficiently. Going into details, the inefficient activity of Protein C might concern its anticoagulant and amidolytic function (subtype IIa) or anticoagulant alone (subtype IIb). Protein C deficiency presents an autosomal dominant inheritance. The disease disturbs regulation of coagulation process and increases the risk of thrombosis even up to three times. Therefore, the heterozygous form of deficiency of Protein C is diagnosed in approximately 5% patients suffering from venous thromboembolism. The homozygous form leads to neonatal haemorrhage, severe purpura and advanced thrombosis, which result in death soon after birth [2,4].

Resistance to Activated Protein C (APC-r)

Activated Protein C resistance (APC-r) is a phenomenon in which proper Protein C does not present activity. It might be confirmed by adding APC to the plasma in which it does not prolong the coagulation time. The test of glycoprotein resistance is used in thrombophilia diagnostics. In most cases, APC-r is a result of presence of Factor V Leiden (about 95%). Other reasons are oral contraceptives, pregnancy, abnormal function of protein S, Factor VIII, prothrombin or its related determinants [2].

Deficiency of Protein S

Protein S (PS) is a single chain glycoprotein produced in liver cells, endothelium, and possibly also in megakaryocytes. Similarly to Protein C, it is vitamin K dependent. It is found in two forms: free protein accounting for 30-40% and bound protein which has affinity to C4b molecule of complement system. PS found in complex with C4b (C4BP) engages with negatively charged phospholipids of cell membranes what triggers the local activity of the entire C4BP. The free form is responsible for the interaction with APC, what accelerates the inhibition of Factor Va and VIIIa activity [2,5].

PS deficiency is inherited in an autosomal dominant way with a different penetration. There are three types of deficiency. Type I is characterized by a decreased total level of Protein S and its free form, while in type II, free Protein S concentration remains normal but its activity is reduced (qualitative defect). Eventually, type III exhibits normal total protein concentration, while free PS level is lower. It is thought that types I and III are phenotypic types of identical mutations. The lack of free PS is associated with a risk of thrombosis due to the unwell action of APC. The consequence of this abnormality is the increased production of thrombin, which is involved in the conversion of fibrinogen into fibrin and, consequently, in the formation of a blood clot. Analogously to protein C, homozygous PS deficiency is presented in neonatal and leads to thrombotic thrombocytopenic purpura and skin necrosis. Heterozygous type contributes to a significantly increased risk of venous thromboembolism. Protein S concentration is reduced in women under 45 years of age, as well as those who use oral contraceptives or are pregnant [2].

Deficiency of Antithrombin

Antithrombin (AT) is a single chain glycoprotein, consisting of 432 amino acids. It belongs to the group of serine protease inhibitors that participates in the inhibition of coagulation process. Inhibitory effects of AT influence active factors IXa, Xa and XIa and thrombin. AT is highly activated by heparan sulfate conjugated to the vascular wall, as well as heparin which present similar to sulfate structure. In the absence of heparin these reactions are extremely slowed [2].

Defects in the structure of the antithrombin protein contribute to the serious dysfunction of the molecule. If the mutation embraces a third region located between the C-terminal segment of the polypeptide and the area affected by thrombin, the inhibitory effect might be abolished. Moreover, the predisposition of binding to the heparin becomes weaker and due to shorter half-life of altered protein, its blood concentration is reduced. Approximately 130 different types of mutations of AT gene have been discovered. Deficiency of AT might be originated from qualitative,

quantitative or qualitative-quantitative defect. Type I is characterized by a decrease in either AT concentration or its activity. Homozygous form of this mutation is lethal, while in heterozygotes the risk of venous thromboembolism is nearly 10 times higher in comparison to healthy population. Type II, which is a lethal defect, is a qualitative failure concerning heparin binding area or the active site of an enzyme. Genetic inheritance of antithrombin deficiency has been described as autosomal dominant [2,4,5].

Increased activity of Factor VIII

Factor VIII is another glycoprotein that participates in the coagulation process. It cooperates with von Willebrand Factor (vWF) forming a complex. Interestingly, an activity of vWF is partially related to the AB0 system. In individuals who have antigen A or B, vWF activity is about 15% higher compared with population of blood type 0. Among others, an intensified activity of Factor VIII is observed, during pregnancy, inflammatory process or estrogen therapies, in highly stressful periods and also in the majority of patients after a deep venous thrombotic episode (usually within the first 3 months) and also among patients suffering from post-thrombotic syndrome [2,6].

Increased Factor VIII activity is significant for thrombotic risk when it exceeds 150%. Studies have shown that this condition leads to 5-6 times higher predisposition to venous thrombosis and 1.3-1.9 times higher risk of an arterial thrombosis. It influences also the risk of recurrence of venous thromboembolism. So far, any defect in the Factor VIII gene, which might affect the concentration of this factor in plasma, has not been detected [2].

Mutation in Factor V gene (Leiden)

Factor V is activated by thrombin and its main function is to enhance the coagulation process in cooperation with activated Factor X, Factor II and phospholipids (so called complex of prothrombinase). Physiologically, the inactivation of Factor V is undertaken by APC, however, in a 5-15% of population, the small spot defect described as Leiden mutation, makes Factor V resistant to APC. The A1691G mutation causes the transition of adenine into guanine (A→G) in 1691 nucleotide, thereby replacing arginine with glutamine. As a consequence, Factor V presents insensitivity on inhibitors and the coagulation process last longer. Furthermore, recent studies have shown the negative effect of this mutation on the inactivation of Factor VIII by the tenase which is a product formed during breakdown of R506 bond in Factor V. The presence of Leiden abnormalities significantly increases the predisposition to venous thrombosis in homozygous (30-120-fold), while in the heterozygotes risk is only 5 times higher than in a population without the defect [2,5,7].

Mutation in the prothrombin gene

The G20210A mutation in the prothrombin gene does not affect its structure. The main change observed in about 87% of population with prothrombin gene defect is elevated concentration of the protein. Probable cause of this phenomenon is enhanced translation efficiency or increased transcriptional mRNA stability what leads the multiplication of thrombin production. The occurrence of this defect has an impact on the 3 times increased risk of venous thrombosis [2,4,6].

Congenital hyperhomocysteinemia

Homocysteine is a sulfuric amino acid, which is a product of methionine metabolism. When the concentration of homocysteine rises above the norm, it exhibits a damaging effect on the endothelium of the blood vessels. This condition increases the predisposition to early development of atherosclerotic lesions, and consequently cardiovascular disease. The elevated levels of homocysteine in the blood are called hyperhomocysteinemia (Hcy) [2].

Hyperhomocysteinemia occurrence is concerned with some hereditary defects. In the vast majority of cases (90-95%) the mutation affects gene of Cystathionine-β-synthase (CBS), which leads to deficiency of this enzyme. Homozygous defects imply a significant increase in homocysteine levels, whereas a heterozygous defect is characterized by a normal concentration of this biocatalyst, however, when the methionine is overloaded, amount of homocysteine increases after 4-8 hours. In other cases, the 667TT mutation of the methylenetetrahydrofolate reductase (MTHFR) gene is present. The role of this enzyme is to participate in the homocysteine remethylation

process which leads to transformation into methionine. Both genetic defects are inherited in an autosomal, recessive manner. Light or moderate hyperhomocysteinemia increases the risk of developing age-related thrombotic episodes. Severe hyperhomocysteinemia increases the predisposition to venous thromboembolism but also myocardial infarction and ischemic stroke. Research does not negate the possibility of Hcy interactions with the other causes of congenital thrombophilia, including the presence of Factor V Leiden [2,5].

Causes of acquired thrombophilia

Acquired hyperhomocysteinemia

Hyperhomocysteinemia may also occur as a result of acquired abnormalities, primarily vitamin deficiencies, coexisting diseases or as a side effects of some drugs. The main factors responsible for this condition are deficiencies of vitamins B6, B12 and folic acid. Examples of medications which carries the risk of Hcy are phenytoin and carbamazepine, while in the list of highly-risk diseases the most important are acute lymphoblastic leukemia, chronic renal failure, Addison-Biermer anemia, hypothyroidism, breast or ovarian cancer and severe psoriasis. Researchers from the Mayo Clinic and the Cleveland Clinic have observed an interesting relationship between homocysteine levels in the body and organ transplantation, mainly of the heart, kidney, liver or lung. For example, in patients 12 months after cardiac transplantation, homocysteine levels were 70% increased with a simultaneous decrease of folic acid and vitamin B6 levels in the blood. Mostly, such a disorder appeared in patients with coexisting vascular complications [2,7]. Increased homocysteine concentrations are described as independent atherogenic risk factors, followed by coronary artery disease, myocardial infarction, and venous thrombosis. Use of folic acid supplements and other B group vitamins can reduce blood homocysteine levels. However, the clinical benefits of this procedure have not been shown [2,7].

Antiphospholipid syndrome

The antiphospholipid syndrome (APS), also called Hughes syndrome, is an inflammatory autoimmune disease of connective tissue. It mainly manifests as vascular thrombosis or recurrent pregnancy loss with a characteristic presence of antiphospholipid antibodies (aPL) in the organism [1,8].

The diagnosis of this disease requires finding one of the clinical and one of the laboratory symptoms. Clinical criteria include:

1. Vascular thrombosis
- one or more vascular thrombosis (excluding superficial venous thrombosis) in any tissue or organ confirmed by objective histological or histopathological examination
2. Obstetric failures
- one or more fetal unexplained deaths of a morphologically normal fetus (documented by ultrasound or direct examination of the fetus) at or beyond the 10th week of gestation
- one or more preterm deliveries of normal newborn before 34 weeks of gestation due to severe preeclampsia, eclampsia or placental insufficiency
- three or more spontaneous abortions before the 10th week of gestation, after exclusion of maternal or paternal chromosome aberrations and endocrine abnormalities or anatomical defects in the mother [1,7,8,9,10].

Laboratory criteria include:

- anti-cardiolipin antibodies (aCL) – medium or high titre of IgG and/or IgM, at least 2 ELISA assays with 12-week intervals,
- antibodies against β2-glycoprotein I – IgG and/or IgM in a medium or high titre, at least 2 ELISA assays with 12 weeks intervals,
- Lupus anticoagulant (LA) – detected on 2 occasions with at least 12 weeks interval [1,7,9,11,12,13,14].

Antiphospholipid antibodies are divided into two classes. The first one is usually represented by IgM type and gathers immunoglobulins which does not need a serum protein cofactor for the combination with phospholipid. Antibodies of the first class

occur naturally after infections. The second class, which is more characteristic for the antiphospholipid syndrome, requires a cofactor, most commonly β2-glycoprotein I, to bind to a phospholipid. The gestation period creates appropriate conditions for the exposure of phospholipid antigens on the cyto- and syncytiotrophoblast. As a consequence, aPL completely block intercellular connections, resulting in the development of an incomplete placenta and impairment of its transport function, as well as insecure implantation of an embryo, or insufficient hormonal synthesis, concerning mainly chorionic gonadotropin and placental lactogen. Direct effects of antiphospholipid antibodies also affect blood coagulation in the uterine and spinal arteries. Another abnormal result of aPL activity is removal of the anticoagulant protection of the protein Annexin V produced in syncytiotrophoblast. Thus, thrombosis and infarcts occur in the placenta and chorionic villi.

The presence of antiphospholipid antibodies might be noticed in other autoimmune diseases such as systemic lupus erythematosus, idiopathic thrombocytopenia, autoimmune hepatitis, but also in syphilis, tuberculosis, HIV infection, cancers and sometimes during chloropromazine and procaquinamide therapies.

In pregnant women, the diagnosis of APS is associated with a risk of venous or arterial thromboembolic disease with a tendency for recurrence, early or late pregnancy loss and preeclampsia or eclampsia. The risk also includes the fetus. It may lead to death, particularly in the second trimester of pregnancy, premature placenta, preterm labor (premature effects), and intrauterine growth retardation (IUGR) [1,6,8,15]. Treatment of APS includes the supply of acetylsalicylic acid, which inhibits apoptosis of trophoblast cells and interrupts activation of endothelium caused by aPL. Low molecular weight heparin remains also in use. It prevents the adverse effects of antiphospholipid antibodies and also shows antithrombotic features. During the International Congress on Antiphospholipid Antibodies, the team of experts has developed a therapeutic procedure in pregnant women with diagnosed antiphospholipid syndrome. Recommendations provide for the therapy with acetylsalicylic acid at a dose of 1 mg/kg body weight per day, starting at the time of conception or immediately after confirmation of pregnancy, ending in 34th week. The implementation of low molecular weight heparin treatment is similar. There is a group of patients who, despite treatment, still suffer from obstetric failures. In their case, alternative high-efficiency (71-90%) therapy using intravenous immunoglobulin (IVIG) can be used. Treatment begins after pregnancy and repeats every 21 days. Currently, glucocorticosteroids are rarely used in pregnant women because of many side effects and greater efficacy of combined therapy (low molecular weight heparin plus low doses of acetylsalicylic acid) [1,7,12,14,16,17].

There is also a severe variant of APS called the catastrophic antiphospholipid syndrome. It is described as a rare case of acute exacerbation of connective tissue disease. It can occur in people who suffer from APS but also in healthy individuals without any aPL found. Infections, pregnancy, surgery or trauma, oral contraceptives, some medicines (e.g. captopril, thiazide diuretics) or withdrawal of anticoagulants may be causative agents. The presence of congenital thrombophilia, mainly deficiency of Antithrombin, Protein S, Protein C and factor V Leiden pose a potential risk. The catastrophic antiphospholipid syndrome is characterized by an acute organ failure – mainly of the kidneys, cardiovascular, respiratory, central nervous system and adrenal glands. A thrombotic thrombocytopenic purpura with hemolytic anemia with positive Coombs test, is reported. Diagnosing a catastrophic antiphospholipid syndrome follows specific criteria including the occupation of at least 3 organs, systems or tissues, with at least one tissue presenting small vessels occlusion (histopathological examination) and the presence of aPL antibodies. Treatment includes anticoagulants, corticosteroids, intravenous immunoglobulins, cyclophosphamide and plasmapheresis [2,18].

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