Inherited Thrombophilia

Subjects: Hematology

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1. Inherited Thrombophilia

Hereditary thrombophilia occurs when an inherited factor requires interaction with components that are inherited or acquired prior to a clinical disorder [1].

The most common causes of hereditary thrombophilia are: antithrombin deficiency, protein C deficiency, protein S deficiency, disturbances in fibrinogen levels, elevated homocysteine levels, factor II mutation (F2 c.*97G > A; previous nomenclature G20210A) and factor V Leiden mutation (HGVS nomenclature: F5 c.1601G > A) [1].

2. Antithrombin Deficiency

Antithrombin (AT) is a thrombin inhibitor and belongs to the serpin family (serine protease inhibitors); these are plasma proteins that inhibit serine proteases to prevent their uncontrolled activity. AT binds to the catalytic site of thrombin and is cleaved, and the resulting fragments remain firmly attached, block the active site and no longer allow fibrinogen to bind. AT activity is potentiated by heparin [2]. The electrostatic interaction between the electronegative heparin groups and the electropositive AT groups (protonated lysine residues) causes a conformational change of the AT, resulting in an increase in its antithrombin activity by about 1000 times. AT also inactivates other serine proteases involved in coagulation, such as factors Xa, XIa, XIIa and kallikrein [2].

AT deficiency is classified into:

- Type I deficiency: reduced synthesis of the molecule (both antigenic and functional activity of AT in the blood are reduced);
- Type II deficiency: molecular defect (AT immunological activity is normal but functional activity is reduced);
- Type III: affected interaction between AT and heparin [1].

In elderly patients with antithrombin deficiency, the risk of thrombosis is increased and long-term administration of anticoagulants becomes unavoidable. Additionally, the incidence of venous thromboembolism is increased in pregnant women with AT deficiency [1]. Patients with type II AT deficiency have a higher risk of developing venous thromboembolism compared to those with type I AT deficiency [1].

3. Protein C Deficiency

Protein C is a protease produced by the liver that contains γ-carboxy-glutamate residues, formed with the participation of vitamin K. It is activated by thrombin. Attached to endothelial thrombomodulin, thrombin modifies its substrate specificity and activates protein C by proteolysis. Activated protein C, in the presence of a cofactor (protein S), degrades factors Va and VIIIa into inactive peptides, leading to coagulation limitation [2].

Hereditary deficiency is caused by a mutation in the PROC gene located on chromosome 2q14.3. Heterozygous and acquired deficiencies are more common than homozygous deficiencies [3]. An inherited or acquired risk factor for thrombophilia is protein C deficiency. People with inherited protein C deficiency have about a 2- to 11- fold increased risk of venous thromboembolism developing [2].

4. Protein S Deficiency

Protein S is a glycoprotein synthesized in the liver and is an important cofactor for protein C activation. Protein S is involved in the coagulation process, having anticoagulant properties both dependent on and independent of active protein C [3]. Approximately 40% of S protein circulates freely in the plasma and 60% with the plasma C4b binding protein (C4b-BP) [3].

Protein S deficiency is a rare genetic disorder of blood coagulation that is caused by a variation in the PROS1 gene. This variation is inherited in an autosomal dominant manner. A recent study published by Juhl et al. reported an association between two novel variants of the S protein gene and protein S deficiency [4].

The following types of S protein deficiency are known:

- Type I: characterized by decreased activated protein C cofactor activity, low values of total S protein and free S protein;
- Type II: characterized by decreased activated protein C cofactor activity, normal values of total S protein and free S protein;
- Type III: characterized by decreased activated protein C cofactor activity, normal values of total S protein and low values of free S protein [3].

Patients with hereditary protein S deficiency have a high risk of venous thromboembolism recurrence. A retrospective study has shown that annual incidences of a first recurrence after the first episode of venous thromboembolism were 8.4% in protein S deficient patients [5].

5. Disturbances in Fibrinogen Levels

Fibrinogen is a glycoprotein with an elongated molecular shape, one of the least soluble in the protein system of the blood and is essential for the formation of fibrin clots. An increased risk of bleeding is associated with acquired and congenital fibrinogen disorders that can lead to a decreased concentration or altered fibrinogen function [6].

Thrombosis as a consequence of fibrinogen malfunction has been explained by two possible mechanisms: one involves abnormal thrombin binding to abnormal fibrin, leading to increased thrombin levels, and the second refers to the function of abnormal fibrin stimulation in fibrinolysis mediated by plasminogen activators [7]. Some patients with disturbed fibrinogen levels may experience thrombophilia and sometimes both bleeding and thromboembolism [6].

6. Elevated Homocysteine Levels

Homocysteine (Hcy) is a non-protein amino acid involved in the metabolism of methionine [8], produced by S-adenosylmethionine (SAM) and S-adenosylhomocysteine (SAH). Homocysteine metabolism involves several enzymes, namely: methionine synthase (MS), methylenetetrahydrofolate reductase (MTHFR), cystathionine β-synthase (CBS), methionine synthase reductase (MSR) and betaine-homocysteine S-methyltransferase (BHMT). Homocysteine can be converted to methionine by remethylation by MTHFR and MS requiring methylcobalamin (vitamin B12). The MTHFR mutation results in reduced enzymatic activity and, consequently, accumulation of homocysteine. Hcy can form cystathionine by condensation with serine, via trans-sulfuration, a CBS-catalyzed reaction dependent on vitamin B6 [9][10][11][12].

At the plasma level, four forms of homocysteine can be found, namely: free Hcy, protein-bound Hcy (S-linked and N-bound), oxidized forms of Hcy, and Hcy-thiolactone. Hyperhomocysteinemia (HHcy) is defined as a plasma level greater than 15 µmol/L [13]. HHcy may be due to genetic defects in the enzymes involved in the metabolism of homocysteine and associated vitamin deficiencies. Elevated homocysteine levels were observed in B12 deficiencies even when folate levels were normal. Only concomitant supplementation of B vitamins (Vitamin B6, Vitamin B12) and folic acid has been reported to be effective in reducing Hcy levels. To date, a large number of studies indicate that Hcy is an independent risk factor for cardiovascular disease and that there is a higher correlation between homocysteine and atherosclerosis levels than between cholesterol and atherosclerosis levels [8][13]. Hcy is thought to be associated with vascular dysfunction through the following mechanisms: generation of reactive species (ROS), triggering/maintaining the inflammatory response; initiation of thrombotic phenomena [10][14]. Endothelial dysfunction is one of the major events in the pathogenic mechanism of cardiovascular disease. In the evolution of this disease, inflammation is the trigger for the process [15][16][17]. Reactive species are among the

compounds present at the site of the inflammation and play multiple roles, including as markers of the intensity of the lesion phenomenon, and molecules involved in defense and/or cell signaling. The literature indicates a link between homocysteine and reactive species. Hcy is a risk factor for thrombophilia and is associated with both venous thrombosis and arterial thrombosis [14]. A study by Ridker et al., over a period of 10 years, showed that the combination of hyperhomocysteinemia and Leiden factor V further increases the risk of venous thromboembolism [18].

7. Factor II Mutation

Prothrombin or coagulation factor II is the precursor of thrombin and is a major coagulation factor. It is synthesized in the liver and involves the participation of vitamin K. Factor II deficiency can be congenital or acquired.

A specific change in the genetic code causes the body to produce too much of the prothrombin protein. The most common point mutation of thrombosis is a factor II mutation known as prothrombin G20210A [19]. The F2 C.*97G > A (previous nomenclature G20210A) variant with autosomal dominant transmission is the second most common hereditary thrombophilia. Assuming that mutations in factor V Leiden and factor II are two genetic risk factors frequently involved in venous thromboembolism, Emmerich et al. [20] studied the risk of its occurrence in patients with both mutations. Their results showed that the frequency of Leiden factor V was lower in patients with pulmonary embolism than in patients with deep-vein thrombosis without pulmonary embolism, and the G20210A mutation was similar in both groups of patients [20].

8. Factor V Leiden

Factor V is a protein in the blood that is involved in the clotting cascade. The proteins involved in the coagulation cascade are activated when it is necessary to stop a hemorrhage. Anticoagulant proteins can deactivate factor V, stopping the formation of thrombi when coagulation is not required.

The point mutation in the factor V gene that leads to the replacement of arginine at position 506 with glutamine is responsible for the resistance to activated protein C. Factor V Leiden is an abnormal protein determined by a single-nucleotide polymorphism (1691G > A) in factor V, and is not susceptible to cleavage at position 506 by activated protein C [21]. Most people with factor V Leiden do not develop thrombophilia, but some may develop thrombosis that leads to long-term health problems and can be life-threatening. Persons with homozygous F2 c.*97G > A or double heterozygous carriers of factor V Leiden and F2 c.*97G > A do not have a risk of developing recurrent venous thromboembolism. Women may have an increased tendency to develop thrombophilia during pregnancy.

The most common inherited form of thrombophilia is related to factor V Leiden, and the second most common genetic form of thrombophilia is related to prothrombin and occurs in approximately 1.7–3% of the general European and American population [22].

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