MODERN VIEWS ON THE DIAGNOSIS OF COAGULOPATHIES: FACTOR II (PROTHROMBIN) DEFICIENCY

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Coagulopathy is a group of disorders characterized by impaired normal blood clotting, which can lead to either excessive bleeding or thrombosis. In the human body, the process of blood clotting (hemostasis) ensures the cessation of bleeding after vascular injury. However, when hemostasis is impaired, various problems arise, such as excessive bleeding or, conversely, an increased tendency to form blood clots.

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Coagulopathy can manifest as a tendency to bleed (e.g., hemophilia, thrombocytopenia) or as an increased tendency to form clots (thrombophilia). In both cases, there is a risk of complications that can lead to serious health consequences.

Rare bleeding disorders (RBDs) include monogenic coagulopathies caused by a deficiency of plasma proteins involved in hemostasis, excluding von Willebrand disease and hemophilia A or B. RBDs include hereditary deficiencies of fibrinogen, prothrombin, and clotting factors V, VII, X, XI, XII, and XIII. The development of RBDs is usually due to recessive inheritance of unique or rare nucleotide changes in the genes encoding coagulation factors or in proteins required for the post-translational modification of these factors. RBDs are most common in ethnic groups with a tradition of consanguineous marriages, which increases the likelihood of homozygous carriage of the defective gene [20,21].

Despite achieved advances, the clinical characteristics of most rare bleeding disorders (RBDs) remain insufficiently documented, and patient management principles have been developed based on results of open observational studies. Due to the rarity of this pathology worldwide, no randomized controlled clinical trials have been conducted [15,16,17,18,19].

Hereditary coagulation factor II (FII) deficiency – prothrombin deficiency – is an autosomal recessive disorder characterized by reduced prothrombin activity in plasma, caused by either quantitative defects (hypoprothrombinemia) or qualitative defects (dysprothrombinemia) in the FII protein structure. The prevalence of FII deficiency in most countries is approximately 1 patient per 2,000,000 population [10,11,12,13,12].

FII is a glycoprotein synthesized in the liver in the presence of vitamin K. Under the influence of activated factor X (FXa) in the initiating phase of the coagulation cascade and the prothrombinase complex (amplification phase), FII is converted into thrombin. Thrombin, in turn, activates other plasma coagulation proteins and platelets, ultimately leading to the formation of a fibrin clot. FII deficiency is caused by variations in the F2 gene, which encodes prothrombin. There is no direct correlation between F2 genotype and disease phenotype [6,7,8,9].

Clinical manifestations. The main manifestation of FII deficiency is bleeding, which can occur spontaneously or after trauma. Hemorrhagic syndrome most commonly presents as mucosal bleeding, soft tissue hematomas of various locations, hemarthroses, bleeding during and after surgical interventions, and severe menstrual bleeding. Less common are gastrointestinal bleeding, hematuria, obstetric bleeding, and bleeding from the umbilical stump. About 7% of patients experience central nervous system (CNS) hemorrhages.

In hypoprothrombinemia with FII activity <10%, bleeding is usually more severe than in cases with FII activity ≥10%, where mild to moderate mucosal bleeding is most typical. Dysprothrombinemia is characterized by a weak correlation between clinical and laboratory phenotypes. Heterozygous carriers of FII deficiency generally have FII activity within 40–75% and are mostly asymptomatic [1,2,3,4,5].

Laboratory diagnosis. Coagulological examination is conducted in stages:

Stage 1. Coagulological screening for suspected hemorrhagic conditions includes:

- Activated partial thromboplastin time (aPTT)
- Prothrombin time (PT)
- Thrombin time (TT)
- Fibrinogen concentration (Clauss method)
- Bleeding time (standardized methods, e.g., Ivy method)
- Instrumental assessment of platelet function

These tests allow determination of the type of coagulation disorder. FII deficiency is characterized by prolonged aPTT and PT, while other above-mentioned parameters remain within normal ranges.

Stage 2. This stage is performed to verify the presence of FII deficiency when prolonged aPTT and PT are detected. A one-stage method for determining FII activity is used, based on calculating the relationship between PT and the percentage content of prothrombin complex factors, constructed using various dilutions of control plasma.

Stage 3. If decreased FII activity is identified, an enzyme immunoassay (ELISA) for FII antigen can be performed to verify hypo- or dysprothrombinemia. Methods using various snake venoms (e.g., *Echis carinatus*, Taipan, and textrarin) allow differentiation of certain variants of dysprothrombinemia.

It is important to note the possibility of acquired FII deficiency in the context of lupus anticoagulant–associated hypoprothrombinemic syndrome, which differs from hereditary FII deficiency in terms of clinical course and the presence of antiphospholipid antibodies [20,21,22,23,24].

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