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CONGENITAL FIBRINOGEN DISORDERS AND GENETIC MUTATIONS

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Congenital fibrinogen disorders (CFD) are a group of diseases that are quite rare. According to clinical manifestations, the following forms of fibrinogen dysfunction are distinguished: quantitative changes (afibrinogenemia and hypofibrinogenemia) and qualitative changes (dysfibrinogenemia and hypodysfibrinogenemia) [1, P.90]. Type I disorders (afibrinogenemia and hypofibrinogenemia) affect the amount of fibrinogen in the blood (fibrinogen levels below 1.5 g/l). Type II disorders (dysfibrinogenemia and hypodysfibrinogenemia) affect the quality of circulating fibrinogen [4].

Fibrinogen is a complex plasma glycoprotein with a molecular weight of 340 kDa. The structure of the molecule forms a hexamer consisting of two sets of three polypeptide chains, Aα, Bβ, and γ, interconnected by disulfide bridges [1]. The mature molecule is encoded by three genes: FGA, FGB, and FGG, located adjacently on chromosome 4q23. The main role of fibrinogen in hemostasis is to strengthen the “plug” of platelets after transformation into an insoluble fibrin polymer by cleavage of fibrinopeptides A and B by thrombin [10]. The fibrin polymer captures erythrocytes and platelets, which leads to the formation of a stable fibrin plaque that stops bleeding at the site of injury [2]. Congenital disorders of fibrinogen can affect the quality and quantity of fibrinogen in plasma [3]. Congenital hypofibrinogenemia is characterized by abnormally low levels of functional and antigenic fibrinogen, usually due to heterozygous mutations in one of the three fibrinogen genes [4]. Fibrinogen during pregnancy is required to support the implantation, proliferation and spread of the trophoblast, as well as for the development of the placenta. During labor, fibrinogen is also required to prevent excessive bleeding caused by separation of the placenta [31, P. 365].

Many CFD patients with low fibrinogen activity are detected spontaneously using coagulation tests in the clinical laboratory, as approximately half of these patients are asymptomatic [2]. Three fibrinogen subunits Bβ (FGB), Aα (FGA), and γ (FGG) are encoded by the fibrinogen genome, which are clustered in a 50 kb region on human chromosome 4 [3]. The most studied mutations in the FGA, FGB and FGG genes over the years have been collected in a common unified global database on human fibrinogen [4], and 47.5%, 19% and 33.5% of mutations were found in the FGA, FGB and FGG

genes, respectively. To date, a total of 81 mutations have been reported in the Chinese population, including 67 missense mutations, 9 frameshift mutations, 4 nonsense mutations, and 1 splicing mutation from 76 probands in 45 families with identified CFD [9]. Most patients with hypofibrinogenemia are asymptomatic; although according to the severity of disorders, some patients still suffer from severe bleeding and at the same time, are not protected from thrombosis [5]. Mutations responsible for hypofibrinogenemia are often localized in the last exon 8 of the FGB gene encoding the C-terminus of the βB chain [6]. Mutations in the FGB gene are of interest because the Bβ chain is thought to be a rate-limiting factor in the production of fibrinogen hexamer in the liver [3,7] and, therefore, can lead to quantitative disturbances of fibrinogen due to impaired secretion. In case of quantitative disturbances of fibrinogen, the mutant chain in the βC domain is retained inside the cell, and only hexamers containing the normal chain are secreted [18].

The gene encoding the fibrinogen Aα chain (FGA) is 7.6 kb in size and consists of 6 exons, the Bβ chain gene (FGB) has 8 exons and occupies an area of 8.0 kb, and the γ chain gene (FGG) covers 8.5 kb and consists of 10 exons [7]. Normal levels of fibrinogen in the blood vary and are usually 1.8–4.2 g/l [8]. Fibrinogen is an acute phase protein that rises in response to various stressful situations such as tissue damage, inflammation, and the accompanying release of cytokines. Fibrinogen expression activation is controlled by interleukin 6 (IL 6) and glucocorticoid signaling pathways [9]. This causes a rapid increase in plasma fibrinogen levels after clotting or bleeding, and also supports wound healing [10]. On the contrary, transforming growth factor β (TGF-β) and cytokines IL4, IL10, and IL13 are negative transcriptional regulators of fibrinogen synthesis [9]. Fibrinogen is predominantly expressed in hepatocytes. However, extrahepatic production has been demonstrated in lung, intestinal, and cervix epithelial cells. The biosynthesis of fibrinogen by megakaryocytes has been discussed for several years, but it is widely believed that the fibrinogen present in platelet alpha granules originates mainly from plasma [11]. Quantitative fibrinogen deficiency is characterized by a concomitant decrease or absence of coagulant activity and immunoreactive proteins. Complete mutational screening of all three fibrinogen genes (FGA, FGB, FGG) is required for molecular diagnosis of congenital fibrinogen disorders [31]. There are two main classes of causative mutations: mutations that produce abnormal protein chains that persist inside the cell; and null mutations with no protein production at all. Hypofibrinogenemia is usually caused by heterozygosity for these mutations [13].

It should be noted that the most frequently mutated residue in the FGA gene is the Arg35 region. One possible mechanism is that Arg35 is part of a thrombin cleavage site at the N-terminus of the α-chain of fibrinogen A, which influences FGA formation. At the same time, the Arg35 mutation can also affect the strength of fibrin strands, which supports platelet aggregation and increases resistance to fibrinolysis. [17,18]. Fibrinolysis is a highly regulated process that begins with fibrin formation and activation of tissue plasminogen activator (t-PA) at plasminogen binding sites. Release of tissue plasminogen activator (t-PA) from endothelial cells leads to the conversion of plasminogen proenzyme into plasmin [20, P. 192]. Hyperfibrinolysis can develop independently of coagulation activation and occurs when plasmin production exceeds the inhibitory effect of α2-antiplasmin. The balance between fibrinolysis activators and their inhibitors is disturbed, which may be a consequence of depletion of the plasminogen activation inhibitor PAI-1 [21]. According to the Human Genome Mutation Database, 15% of all missense mutations are associated with an arginine residue [9, P. 18, 10]. Replacing arginine with cysteine results in the loss of the guanidine moiety to arginine, thereby changing the functions of the protein. Interactions of guanidine fragments, such as H-bridges and van der Waals forces, disappear in this process [11]. The situation is similar for the Arg301 region in the FGG gene. 34 mutations were identified in the FGG gene and most of them were present in the Arg30 region. The mechanism underlying the Arg301 mutation is an increase in thrombin levels due to impaired fibrinogen-thrombin binding capacity and a decrease in tissue plasminogen activator-mediated fibrinolysis as a consequence of molecular changes in fibrin [12]. Thrombin binds to its substrate fibrinogen via the fibrinogen recognition site in thrombin, the so-called exosite 1 [16]. The fibrin clot itself also has significant thrombus-binding potential. This non-substrate binding potential of fibrin to thrombin is called antithrombin I [18]. Antithrombin I (fibrin) is an important inhibitor of thrombin formation, which acts by sequestering thrombin in the forming fibrin clot, as well as by reducing the catalytic activity of fibrin-bound thrombin. Intravascular thrombosis may be the result of the absence of antithrombin I (as in afibrinogenemia), due to a reduced content of the γ'-chain in plasma, or impaired thrombin binding to fibrin, as is observed in some dysfibrinogenemias [19].

A study in the Slovenian cohort identified a new nonsense mutation in the FGB gene resulting in mild hypofibrinogenemia in two unrelated patients [14, 15]. According to the database of mutations in fibrinogenic genetic variants (http://site.geht.org/base-fibrinogene/), most causative mutations in afibrinogenemia have been identified in the

FGA gene [11]. Mutation variants of fibrinogen in hypofibrinogenemia are localized in the FGG gene, and only 26.6% of causative mutations are localized in the FGB gene [26]. There are several mechanisms that can lead to impaired fibrinogen synthesis at several levels: DNA, RNA or protein in general. Various causes have been reported, such as an assembly defect, reduced synthesis, secretion or increased degradation of intracellular protein, or a combination of these defects [32,33]. Congenital quantitative disorders of fibrinogen are most often caused by null mutations, as well as missense mutations, many of which are grouped in exon 8 of the FGB gene, which encodes a highly conserved C-terminal globular domain of Bβ fibrinogen [30]. It is known that mutations at this site strongly affect the assembly and secretion of fibrinogen [14]. FGA and FGG are transcribed from the reverse strand in the direction opposite to the FGB gene. Each gene is individually transcribed and translated to form nascent polypeptides of 644 amino acids (Aα), 491 amino acids (Bβ), and 437 amino acids (γ). FGA alternative splicing produces the minor extended isoform (Aα-E), while FGG alternative splicing produces the γ' isoform. The rate of catabolism is 25% per day [23]. In addition to plasma fibrinogen, blood contains an internalized (internalization from Latin interims - internal, the process of mastering external structures, as a result of which they become internal regulators) intracellular pool of fibrinogen, which is stored in platelet α-granules. Both megakaryocytes and platelets are able to internalize plasma fibrinogen through the fibrinogen IIb/IIIa glycoprotein receptor (GpIIb-IIIa; αIIbβ3) [24]. The transformation of fibrinogen into a fibrin clot [15, 16] occurs in three separate phases: fibrin monomers are formed; (2) self-assembly of fibrin units to form an organized polymeric structure; and (3) covalent crosslinking of fibrin by factor XIIIa [26, 37].

Dysfibrinogenemias and hypodysfibrinogenemias are usually associated with autosomal dominant inheritance caused by heterozygosity for missense mutations in the coding region of one of the three fibrinogen genes and are therefore more common than type I disorders. Dysfibrinogenemia was first reported in 1958, and more than 500 cases have been reported to date. Dysfibrinogenemia is usually detected incidentally due to abnormal coagulograms or because a case of this pathology was previously detected in the family [1-4]. However, some patients may experience bleeding, thromboembolic complications, or both. A study of more than 260 cases of dysfibrinogenemia showed that 55% of patients had no clinical complications, 25% had bleeding, and 20% had a tendency to thrombosis, mainly venous after surgery or in the postpartum period [22]. Two mechanisms may explain most cases of thrombosis associated with dysfibrinogenemia: abnormal fibrinogen cannot bind thrombin, resulting in increased

thrombin levels; abnormal fibrinogen forms a fibrin clot that is resistant to degradation by plasmin. In recent studies, a high prevalence of dysfibrinogenemia has been noted among patients with chronic thromboembolic pulmonary hypertension [38]. Women with dysfibrinogenemia in most of the presented clinical cases suffer from spontaneous abortions, recurrent miscarriage and postpartum hemorrhage.

In most patients, hypofibrinogenemia is diagnosed incidentally during routine coagulation screening [1]. Most episodes of bleeding are caused by trauma or surgery [16]. Pregnancy and childbirth are high-risk situations in women with hypofibrinogenemia, with an increased risk of miscarriage, metrorrhagia, and placental abruption [17]. Fibrinogen replacement therapy is effective in treating acute bleeding or preventing hemorrhagic complications [18,19]. Indeed, in contrast to dysfibrinogenemia and hypodysfibrinogenemia, in hypofibrinogenemia there is no mutant fibrinogen variant in the bloodstream, so differences in clot properties are not associated with fibrinogen mutation [23,25]. However, other proteins or common polymorphisms, such as FXIII Val34Leu, can affect fibrinolysis, which is associated with a decrease in its rate [24]. On the other hand, the rate of fibrinolysis correlates with the concentration of fibrinogen [25]. The literature describes five heterozygous nonsense mutations associated with hypofibrinogenemia in the C-terminal domains of the Bβ chain (Gln339, Gln393, Trp402, Cys407, and Trp440) [26–30], located predominantly in exon 8 of the FGB gene. In four genetic variants, the phenotypic presentation was severe bleeding, similar to that commonly seen in patients with afibrinogenemia (such as epistaxis, umbilical cord bleeding, splenic rupture, and intracranial hemorrhage). Patients with a nonsense mutation in the C-terminal domain of the Bβ chain had moderate hypofibrinogenemia; four patients with the Bβ Gln393 nonsense mutation also had moderate hypofibrinogenemia [27]. In addition to bleeding symptoms, pregnancy complications (recurrent pregnancy loss in the first trimester) have also been reported in a patient with a Bβ Cys407 mutation [30]. Protein modeling allows a better understanding of the molecular anomaly underlying the fibrinogen defect [28].

Using modeling, it was revealed that a new nonsense mutation will lead to changes in the secondary structure of the molecule with the loss of three β-sheet structures (Gly420-Tyr422; Trp444-Ser446; Lys449-Phe457). It is also expected that some hydrogen bonds within the molecule will be affected, especially those associated with missing amino acids and surrounding residues (for example, between Arg448 and Glu315 or Tyr416 or between Tyr445 and Trp317) [34]. All these mutations are located at the globular C-terminus of the Bβ chains of the FGB gene. The βC domain plays a

key role in the control of fibrinogen secretion [31]. In their study, using a transfected cell model system, Vu et al. showed that deletion of more than seven residues from the C-terminus of the Bβ chain leads to inhibition of fibrinogen secretion. The collected mutant fibrinogen was found within the cell extracts but not in the mutant hexamer retention medium. A greater degree of truncation suggests an increased instability of these truncated chains [35]. Overall, these results suggest that Bβ Trp444Ter fibrinogen secretion is also prevented by an endoplasmic reticulum quality control mechanism consistent with the observed phenotype, i.e., mild hypofibrinogenemia when the mutation is in heterozygosity [38,39].

In reported cases, even low levels of mutant fibrinogen can promote hypercoagulability by affecting fibrin clot properties such as fibrinolysis [36]. The literature describes cases of thromboembolism in patients with congenital quantitative disorders of fibrinogen, who were injected with fibrinogen concentrate. In the studies of Peyvandi et al. a group of scientists found that in fibrinogen deficiency there is a strong relationship between the activity of converting fibrinogen to fibrin and the clinical phenotype of bleeding, despite the fact that correlations between genotype and phenotype are difficult to establish. In addition, some mutations may increase the tendency to bleed, while others may predispose to thrombosis [25]. Five genetically determined variants of dysfibrinogenemia associated with thrombophilia and various pathogenic mechanisms have been reported in the literature, including: structural changes in the fibrin network, increased thrombin levels, due to impaired fibrinogen binding; a decrease in fibrinolysis as a result of impaired binding of tissue plasminogen activator or plasminogen to dysfunctional fibrinogen [23].

However, unlike afibrinogenemia, the clinical picture in patients with dysfibrinogenemia varies greatly [30]. Management of obstetric problems should be individualized according to the clinical phenotype of the fibrinogen gene mutation. Genetic data can help to better predict the risk of bleeding severity and thrombosis [10].

Despite a wealth of information on the epidemiology and genetics of hereditary fibrinogen disorders, which allows us to better understand abnormalities in the molecular structure of fibrinogen and more accurately define the clinical manifestations of these disorders, predictions regarding individual phenotypes remain uncertain [1-10]. Congenital anomalies of fibrinogen have a huge variety in expressivity and penetrance. The clinical phenotype of patients with hypofibrinogenemia is very heterogeneous. With hypofibrinogenemia, some patients experience significant episodes of bleeding; others may experience minor bleeding, while some remain asymptomatic all their lives [35-39].

Paradoxically, however, thrombotic events have been reported in diseases with a bleeding tendency. Some patients with hypofibrinogenemia develop venous or arterial thrombosis with or without fibrinogen replacement therapy. Thrombosis and obstetric complications also occur in patients with hypofibrinogenemia, and their management requires a multidisciplinary approach [13].

A more accurate determination of changes in the molecular structure, properties and amount of fibrinogen and their relationship with the clinical phenotype will help doctors better understand the pathophysiology of the defect and predict the clinical manifestation of a particular molecular abnormality in the future. Since CFD is a rare disease, there is not enough information in the scientific literature to accurately examine how this pathology will present itself. Whether CFD manifests as bleeding or thrombosis depends on various exogenous and endogenous risk factors [36].

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