DYSFIBRINOGENEMIA: FROM BLEEDING TENDENCY TO THROMBOEMBOLIC DISORDERS

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ABSTRACT

Dysfibrinogenaemias are congenital or acquired qualitative abnormalities of fibrinogen that are characterized by low plasma clottable fibrinogen levels (usually < 1.5 g/L) and normal fibrinogen antigen concentrations. In clinical practice the diagnosis of dysfibrinogenemia is based on the detection of prolonged thrombin time, the most sensitive screening test, and low ratio of clottable fibrinogen to its antigen (about 1:2). The ultimate diagnosis, however, is established based on molecular tests. Dysfibrinogenemia is in most cases asymptomatic and detected incidentally. Clinically overt manifestations of dysfibrinogenemia involved bleeding, usually related to trauma, surgery, or childbirth (in ca 20 % of cases) and/or thrombosis, arterial or venous (in ca 25 % of cases). An increased risk of miscarriages, umbilical cord bleeds and prolonged wound healing is also frequently reported in dysfibrinogenemic individuals. More than 450 congenital dysfibrinogenemias caused by heterozygosity for a mutation within any of the three fibrinogen chain genes (*FGA*, *FGB*, *FGG*) have been reported worldwide. Dysfibrinogenemias are associated predominantly with defective fibrinopeptide release and/or with retarded fibrin polymerization. Acquired dysfibrinogenemia largely resulting from posttranslational modifications of fibrinogen molecules, predominantly oxidation, glycation, or homocysteinylation, can also be detected in several disease states, including liver disease, multiple myeloma, autoimmune disorders, and also in atherothrombotic cardiovascular disease. Inherited dysfibrinogenemia should be considered in patients with a personal and familial history of bleeding or thrombosis when

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No conflict of interest to declare

other causes of these disorders have been excluded.

Key-words: Bleeding, dysfibrinogenemia, fibrinogen, mutation, thrombosis

FIBRIN CLOT GENERATION

Fibrinogen is a 340-kDa glycoprotein, synthesized in the liver and encoded by three genes (each one for each chain) located on chromosome 4. Under physiological conditions, fibrinogen is present in plasma at concentrations of 1.8-3.5 g/L (6-12 μM). A fibrinogen molecule is a hexamer composed of three paired polypeptide chains $(A\alpha, B\beta, \gamma)_2$ crosslinked by 29 disulfide bonds. Fibrinogen contains three main structural regions connected by α-helical coils: a central E domain with N-termini of all six polypeptide chains (with fibrinopeptides A, B) and two outer D domains with C-termini of Bβ and γ chains. The C-termini of the Aα chains are globular structures situated near the central E domain.

Fibrin clot formation results from a series of rapid events initiated by thrombin cleavage of the Aα and Bß chains of fibrinogen. Thrombin binds to the central region of fibrinogen. Thrombin-mediated release of fibrinopeptide A (FPA) and – much slower – B (FPB) from the amino--termini of the Aα– and Bβ-chains of fibrinogen, respectively, results in the formation of fibrin monomer with the structure $(\alpha, \beta, \gamma)_2$ that can polymerize via noncovalent interactions between the D domains and the central E domains of fibrin monomers. This process results in the formation of double-stranded fibrils that associate laterally forming thick fibers. Cleavage at residue Aα-16 releases fibrinopeptide A to form fibrin I. The release of two fibrinopeptides A exposes a site in the E domain that aligns with a complementary site in the D domain to form overlapping fibrils. This is followed by cleavage at Bß-14 and the subsequent release of the two fibrinopeptides B, resulting in fibrin II formation. This release most likely allows for lateral aggregation of the protofibrils[1,2]. The degree of lateral strand association contributes to the tensile strength of the clot, but its resistance to plasmin degradation is influenced mainly by covalent cross-linking. Cross-links are formed by the action of activated factor (F)XIII, a transglutaminase enzyme whose formation from zymogen FXIII is catalyzed by thrombin[3]. The covalent cross-linking of the γ chain carboxyl--terminal fragments occurs between lysine at position 406 of one chain and glutamine at position 398/399 of another. Intermolecular cross--linking between α chains in their mid– and carboxyl-terminal portions results in oligomer and polymer formation, in a much slower process comparing with γ-dimerization. Other cross-links, γ–multimers are formed through interfibril band formation in an even slower reaction and the formation of multimers is essential for the structural integrity of a clot[3]. Two glutamine and one lysine sites exist in the γ-chain, whereas there are four of them for glutamine and at least 15 for lysine in the α-chain, which enables to form a highly complex branched structure resistant to lysis[3].

FIBRIN DEGRADATION

Dissolution of a fibrin clot results from the interaction of tissue plasminogen activator (tPA), a serine protease released by endothelial cells, and plasminogen on a fibrin surface. A release of tPA is stimulated by a number of factors, including thrombin, or high shear stress. The presence of fibrin greatly accelerates by at least two orders of magnitude plasmin generation catalyzed by tPA, which is limited proteolysis of plasminogen[4]. Plasmin cleaves Lys-Arg bonds in the fibrin molecules and accounts for clot degradation. In the absence of inhibitors, cleavage of the amino terminal portion of plasmin produces three similar forms of plasmin collectively called Lys-plasmin[4]. A family of serine protease inhibitors inhibits fibrinolysis via formation of an irreversible complex with the active site of plasmin. The major inhibitor, α_2-antiplasmin, which circulates in plasma at high concentrations, is highly effective in the neutralization of plasmin. However, plasmin bound to fibrin is protected from the action of α_2-antiplasmin. Plasminogen activator inhibitor-1 (PAI-1), a key physiological inhibitor of tPA, is released from several cells and platelets when inflammatory cytokines, thrombin or lipoproteins are up-regulated. The thrombin activatable fibrinolysis inhibitor (TAFI) attenuates plasminogen activation[4]. Once activated by thrombin, TAFI removes plasmin-binding carboxy-terminal lysine residues on soluble fibrin degradation products, resulting in increased stability of thrombi[4]. Plasmin-mediated fibrin degradation leads to the release of specific crosslinked fibrin degradation products, termed D-dimers, which are a sensitive marker of in vivo fibrin formation and lysis.

DYSFIBRINOGENEMIAS

Dysfibrinogenemias are congenital or acquired qualitative abnormalities of fibrinogen that are characterized by low plasma clottable fibrinogen levels (usually < 1.5 g/L) and normal fibrinogen antigen concentrations (see below). Dysfibrinogenemias can be classified into three categories based on abnormalities in fibrin clot formation associated with (1) defective fibrinopeptide release, (2) retarded fibrin monomer polymerization, and (3) deficient fibrin cross-linking. Most known dysfibrinogenemias result in two or more functional defects, commonly both abnormalities in fibrin polymerization and fibrinopeptide release. Some investigators divide dysfibrinogens into two groups: those with altered FPA and FPB release and those without such defect. The former group of abnormalities affects the amino-terminal regions of the α and β chains, while the other group comprises heterogeneous defects located in various segments of the fibrinogen molecule, particularly within the γ chain.

Dysfibrinogenemia can be congenital or acquired. The first group of fibrinogen disorders represent more than 450 genetically determined alterations in fibrinogen structure described to date. Dysfibrinogenemias are most commonly asymptomatic and detected incidentally at the age of a few months to more than 70 years, mostly in adults. Clinically

symptomatic congenital dysfibrinogenemias may be associated with either thrombotic (ca 20% of all cases) or bleeding (25%) tendency, or both[5]. It is estimated that about 25% of patients with a bleeding history experience a thrombotic episode during lifetime[5]. Thrombotic or bleeding events in patients with dysfibrinogenemia are episodic in nature and occur in other family members, therefore dysfibrinogenemia represents a rare cause of familial thrombophilia affecting the arteries or veins or bleeding diathesis. Moreover, an increased risk of pregnancy complications, including miscarriages, as well as an increased prevalence of umbilical cord bleeds and prolonged wound healing have been observed in some dysfibrinogenemic individuals[6].

LABORATORY EVALUATION

In a patient with a suspicion of dysfibrinogenemia, both congenital and acquired, the following tests should be performed: prothrombin time (PT), activated partial thromboplastin time (aPTT), thrombin time (TT) and fibrinogen level (functional activity and antigen concentration). These tests are sensitive but lack specificity[7].

Thrombin time is the most important screening test (Fig. 1). Its prolongation is usually observed when fibrinogen activity falls below 1.0 g/L. Similarly, PT is prolonged if clottable fibrinogen level falls below 1.0 g/L, while aPTT exceeds the upper limit of the normal range infrequently in dysfibrinogenemia, at fibrinogen concentrations below 0.6 g/L[7].

TT measures the rate of fibrin clot formation after addition of a standard concentration of thrombin to plasma. Dysfibrinogens often prolong TT by inhibiting FPA and/or FPB release or by inhibiting fibrin monomer polymerization. Thrombin time is sometimes substituted or supplemented by reptilase time (RT) that measures the rate of fibrin clot formation after addition of reptilase (a snake venom enzyme that cleaves only FPA from fibrinogen) to citrated plasma. This test is unaffected by heparin and should be used when there is suspicion of sample contamination with heparin or dysfibrinogenemia when TT is normal.

Fibrinogen functional activity assay (the Clauss method) measures the rate of clot formation after adding of high thrombin concentration to plasma. Fibrinogen antigen levels are determined using immunologic methods, e.g. nephelometry, radial immunodiffusion or an enzyme-linked immunosorbent assay. Normal plasma fibrinogen concentrations, detected using both types of the methods, are mostly 1.5-3.5 g/L. Fibrinogen activity and concentration should be measured in the same sample, because a fibrinogen plasma level changes in response to infection, injury or various stressors.

Dysfibrinogenemia is characterized by significant discrepancy between the levels of clottable fibrinogen (determined most frequently using the Clauss method) and immunologically measured fibrinogen. Functional fibrinogen levels are typically lower than its antigen concentration, with fibrinogen activity-antigen ratio being in most cases approximately 1:2 (Fig. 1). This ratio is diagnostic in more than 90 % of dysfibrinogenemic subjects. This pattern is different

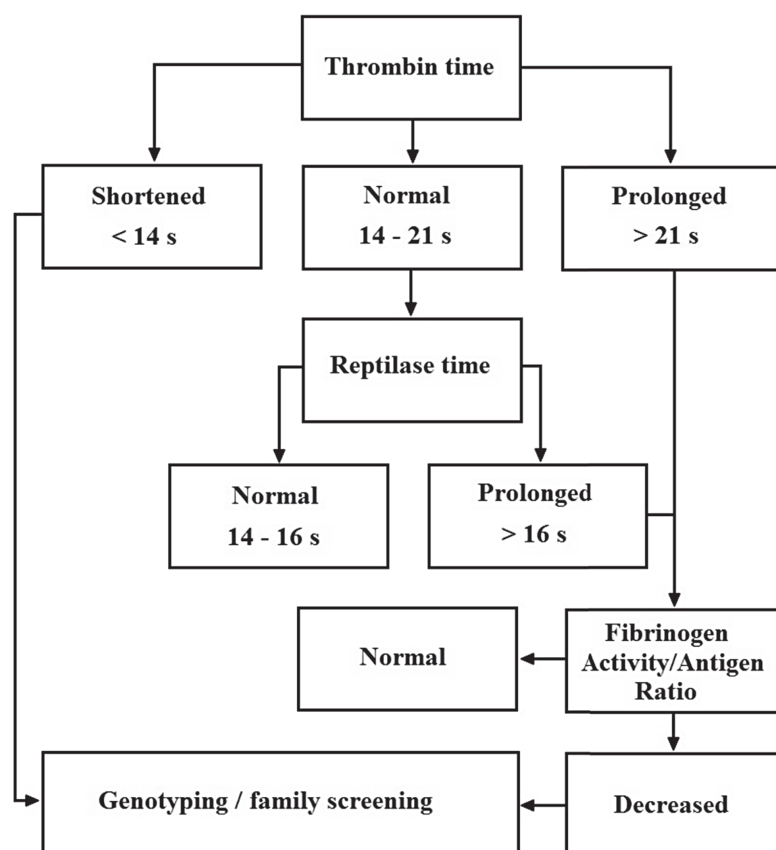

Fig. 1 – Algorithm for laboratory diagnosis of dysfibrinogenemia. In case of shortened thrombin time we should also exclude dextran or hydroxyethyl starch use.

from that observed in hypofibrynogenemia where fibrinogen activity and antigen are similar and range between 0.5 g/L and the lower limit of normal range of the laboratory (usually 1.5 g/L). In hypodysfibrinogenemia both the quantitative and the qualitative defects coexist and fibrinogen levels determined using a coagulation-based and immunologic assays are in the range of 0.5-1.2 g/L. It should be mentioned that sometimes clottable fibrinogen levels could be low-normal as a result of an acute phase reaction during infection, inflammatory disease, trauma or surgery; a significant increase in fibrinogen concentrations can be observed also in most dysfibrinogenemic subjects and this could hamper establishing a proper diagnosis.

Of note, routine coagulation laboratory tests often do not provide the clear-cut diagnosis. PT and aPTT may remain in the normal range as well as thrombin time. Fibrinogen activity is typically decreased but may be normal (< 1.5 g/L), however usually markedly lower than plasma fibrinogen antigen concentrations. Moreover, the sensitivity of the fibrinogen activity/antigen ratio in dysfibrinogenemia depends on the reagents and the specific mutation, therefore the ultimate diagnosis should be established using genetic analysis of the fibrinogen genes (Fig. 1). Examples of results of diagnostic tests in dysfibrinogenemias

diagnosed in Poland have been shown in Table 1.

Fibrin clot structure and function can be assessed using several measures, including (1) clot permeability, or Darcy constant K_s (an indicator of the pore size), calculated based on the volume of buffer flowing through the fibrin gel in a given time period; (2) fiber mass-length ratio, based on the permeability and a fibrinogen molar concentration; (3) the lag phase by turbidimetry that reflects the time to the start of lateral fibril aggregation; (4) maximum absorbancy of the growing clot that reflects an average fibrin fiber size and the number of protofibrils per fiber[8]. Clot turbidity is related to the number of fibrin fibers, their thickness and branching points, as well as to the uniformity of fiber distribution. Viscoelastic properties of clots, such as the dynamic storage modulus, the loss modulus, the tau delta (an indicator of the clot irreversible deformation), and clot stiffness, can be assessed using a Plazek torsion pendulum.

Imaging techniques used to assess fibrin clot structure include scanning or transmission electron microscopy and confocal microscopy. Scanning electron microscopy (SEM) that is the most commonly used technique in microscopic evaluation of fibrin permits the measurement of fiber diameter, pore size and branching angles. However, this technique requires fixing a clot mostly by permeating it with glutaraldehyde solution with the subsequent dehydration.

Fibrin clot properties can be studied not only in solutions of purified or recombinant fibrinogen, but also in citrated plasma upon addition of varying concentrations of thrombin and calcium. From a pathophysiological point of view, plasma-based assays appear to be closer to the in vivo situation where fibrin(ogen) is subject to modulatory effects of other circulating proteins or other molecules. However, the most common approach to assess fibrin structure in dysfibrinogenemic subjects is turbidimetric evaluation and SEM analysis of a fibrin clot formed from purified fibrinogen and/or less frequently, recombinant dysfibrinogens.

In most clot lysis assays, recombinant t-PA at varying concentrations, ranging usually from those encountered during lytic therapy in vivo to 10-fold higher values, is added simultaneously with thrombin. Slower fibrinolysis occurs in tight fiber

Table 1 – Dysfibrinogens described in Polish patients

Type of mutation	Prothrombin time [s]	Activated partial thromboplastin time [s]	Thrombin time [s]	Fibrinogen (the Clauss method) [g/L]	Fibrinogen (nephelometry) [g/L]	Symptoms
Fibrinogen Krakow γ(Asn325Ile)[27]	not reported	34.0 (N: 28-40)	21.5 (N: 14-21)	0.62 (N: 1.8-3.5)	1.16 (N: 1.8-3.5)	No bleeding Venous thrombosis
Fibrinogen Zabrze γ(Arg275His)[19]	12.9 (N: 10-15)	30.2 (N: 26-36)	33.0 (N: 14-21)	0.86 (N: 1.8-3.5)	2.8 (N: 1.8-3.5)	No bleeding No thrombotic events
γ(Ala82Gly)[6]	16.6 (N:12-18)	35.10 (N: 30-40)	18.0 (N:10-18)	0.93 (N: 1.8-3.5)	1.5-2.0 (N: 1.8-3.5)	Severe bleeding Miscarriages

meshworks compared with clots of thicker, looser fibers despite the fact that individual thicker fibers are lysed at a slower rate than thin ones are[9].

INHERITED DYSFIBRINOGENEMIAS

Genetic abnormalities in patients with dysfibrinogenemia have been found in all three fibrinogen genes (4q28.1, 4q28.2, and 4q28.3 for *FGG*, *FGA*, and *FGB*, respectively) and identified in the majority of cases as missense, nonsense, or frameshift mutations as well as splice-side abnormalities or rarely as deletions (listed at http://www.geth.org/databaseang/fibrinogen).

Most of subjects with dysfibrinogenemia are heterozygous for the given mutation, with a mixture of abnormal and normal fibrinogen molecules in circulating blood. Examples of symptomatic dysfibrinogens and the respective localization of the underlying mutations are shown in Fig. 2.

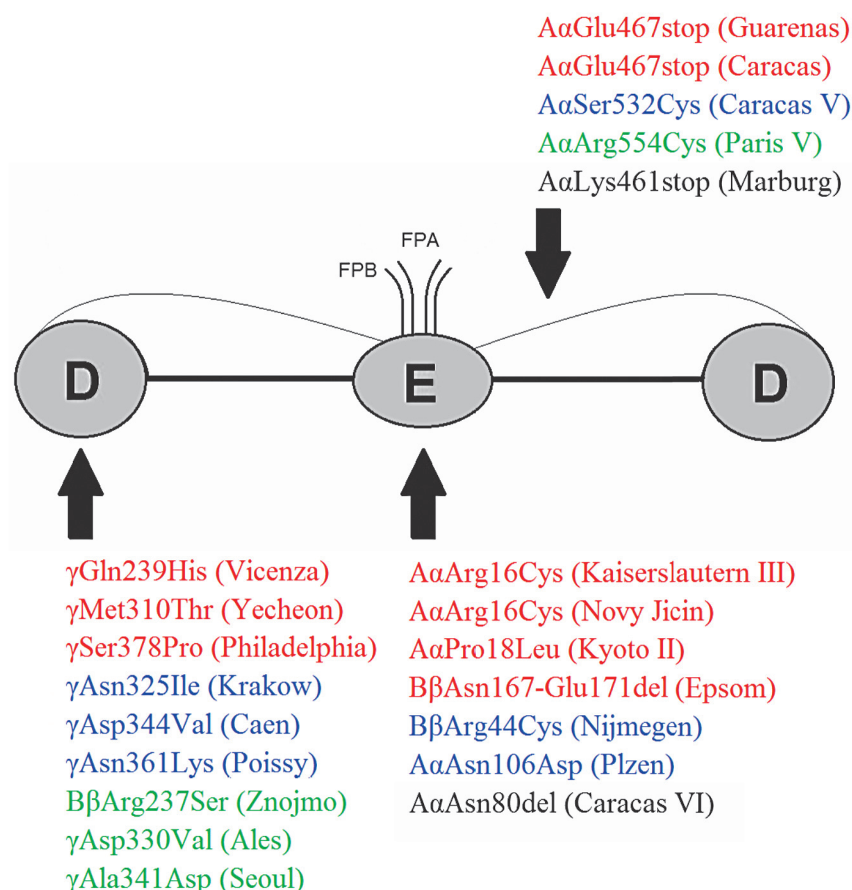

Fig. 2 – Scheme of the domain structure of the fibrinogen molecule with the location of selected mutations resulting in symptomatic dysfibrinogenemias. A central E domain contains N-termini of six polypeptide chains (Aα,Bβ,γ)2 with fibrinopeptides A (FPA) and B (FPB), and two outer D domains contain C-termini of the Bβ and γ chains, together with the αC domain (residues 111 to 610 in the Aα chain). Mutations shown in red are associated with bleeding, in blue are associated with venous thrombosis, in green are associated with arterial thrombosis, and those in black are associated with both bleeding and thrombosis (for details see the main text).

Aα chain mutations

Fibrinogens with Aα chain mutations are often associated with fibrinopeptide release and are often related to bleeding tendency. The most common α-dysfibrinogens are caused by mutations at Arg16 or Pro18 (Fig. 2).

Fibrinogen Caracas VI[10] (deletion of AαAsn80) was associated with mild bleeding in young patient, and several years after with thrombotic event. Caracas VI fibrinogen was characterized by impaired fibrin polymerization, abnormal permeability, decreased clot stiffness due to disrupted alpha-helical coiled-coil structure. Fibrinogen Plzen[11] (AαAsn106Asp) was associated with thrombotic events due to delayed polymerization, slower tPA--initiated fibrin clot lysis and altered platelet aggregation.

Fibrinogen Kaiserslautern III[12] (AαArg16Cys) was identified in a man with prolonged PT and a mild bleeding tendency. The rate of FPB release by thrombin was slightly delayed while the release of FPA was only half the normal amount caused by a mutation in a thrombin cleavage site.

Fibrinogen Novy Jicin[13] (AαArg 16Cys) was associated with hemorrhagic complications in 12-year-old girl. TT (70.8 s) and RT (> 180 s) were prolonged, clottable fibrinogen concentration was decreased (0.3 g/L). The kinetics of fibrinopeptide release and fibrin polymerization were impaired. Fibrinogen Kyoto II[14] (AαPro18Leu) was diagnosed in a women with bleeding tendency. PT and aPTT were prolonged, release of fibrinopeptides was normal, but fibrin monomer polymerization was impaired. A clottable fibrinogen concentration was decreased (0.64 g/L), while a fibrinogen concentration determined by immunologic method was normal (2.16 g/L). This mutation in the amino-terminal of Aα-chain occurs at the polymerization site.

Bβ chain mutations

Abnormal fibrinogens caused by Bβ chain mutations are rare and often characterized by concomitant secondary abnormal structure in the N-terminal region of α-chain or C-terminal region of γ-chain.

Fibrinogen Nijmegen[15] (BβArg 44Cys) was found in a patient with venous thrombosis. Fibrin clot lysis was prolonged and tPA plasminogen activation was impaired which suggested attenuated fibrinolysis. TT was normal, reptilase time was slightly prolonged, clottable fibrinogen concentration (1.2 g/L) was lower than that determined immunologically (3.5 g/L)[16]. Fibrinogen Nijmegen can be linked to albumin or other proteins by disulfide bonds and generate high molecular weight complexes due to additional free sulfhydryl groups in the dysfibrinogen molecules[16].

Fibrinogen Znojmo[17] (BβArg 237Ser) was diagnosed in a patient with thrombosis and pulmonary embolism. FPA, and FPB release were found to be normal but fibrinolysis was impaired and clot morphology (slightly increased fibril diameters, abrupt fibril terminations) was abnormal.

γ chain mutations

Dysfibrinogenemias caused by γ chain mutations predominantly in the carboxyterminal region of this chain are common, but only about 5 % of the patients present with bleeding and about 30 % with thrombosis. The majority (65 %) remain asymptomatic[18]. Gamma dysfibrinogens are typically associated with impaired polymerization of fibrin monomers and normal fibrinopeptide release. All the γ-dysfibrinogens described are characterized by prolonged TT. The most common γ-dysfibrinogen is caused by mostly asymptomatic mutations at Arg275, largely Arg275His (e.g. Fibrinogens Peruggia I, Bergamo I, Barcelona IV, Osaka I, Zabrze [19]: Table 1) or Arg275Cys (e.g. Osaka II, Tokyo II, Milano V, Baltimore IV)[18].

Examples of symptomatic dysfibrinogens have been presented below (Fig. 2).

Fibrinogen Ales[20] (γAsp330Val) was diagnosed as homozygotic dysfibrinogenemia in a man with a history of two thrombotic strokes before the age of 30. Thrombin-induced fibrin polymerization was impaired, and no polymerization in the presence of reptilase occurred. Plasma

clottable fibrinogen (the Clauss method) was very low (0.20 g/L); fibrinogen determined immunologically was normal (3.05 g/L). The polymerization defect was characterized by a defective site "a" resulting in an absence of interaction between sites "A" and "a".

Fibrinogen Caen[21] (γAsp344Val) was noted in a 5-year-old with post-operative deep-vein thrombosis. This mutation is directly involved in calcium binding and is associated with abnormal thrombin binding, abnormal clot formation, and decreased fibrinolysis.

Fibrinogen Poissy II[22] (γAsn361Lys) was diagnosed in a pregnant woman with disseminated intravascular coagulation and abruptio placentae and also in asymptomatic members of patient family. The FPB release by thrombin was impaired and related to a delayed thrombin-induced fibrin polymerization.

Fibrinogen Vicenza[23] (γGln239His) was diagnosed in a patient with mild bleeding diathesis due to defective fibrin monomer polymerization.

Fibrinogen Yecheon[24] (γMet310Thr) was found in a patient with a history of bleeding in the neonate period. The PT was prolonged, fibrinogen activity was lower than the detection limit (< 0.25 g/L), while the fibrinogen antigen level was normal (4.37 g/L). γMet310Thr mutation results in the γAsn308 N-glycosylation which inhibits normal fibrinogen activity.

HYPODYSFIBRINOGENEMIAS

More than 25 abnormal fibrinogen variants have been reported in patients with low levels (< 1.5 g/L) of dysfunctional fibrinogen determined using functional tests and immunological methods (hypodysfibrinogenemia). Most hypodysfibrinogenemias are caused by defects in the C-terminal region of the γ-chain that encompasses several functionally important sites, including the calcium binding (γ 311-336) and polymerization (γ 374-396) sites.

Fibrinogen Philadelphia[25] (γSer 378Pro) was described in a family with a history of bleeding and was associated with prolonged TT, abnormal fibrin polymerization probably due to a major defect in lateral aggregation, and increased catabolism of the abnormal fibrinogen. Fibrinogen Epsom[26] (BβAsn167--Glu171del) was associated with both increased clotting times and low functional and immunological fibrinogen concentrations, which led to pregnancy-associated bleeding episodes.

Fibrinogen Krakow[27] (γAsn325Ile) was reported in a young woman as a mutation associated with deep-vein thrombosis following surgery at the age of 16 with subsequent mild post--thrombotic syndrome (Table 1).

Fibrinogen Marburg[28] (AαLys 461stop) was found in a young woman suffered from a uterine hemorrhage after Caesarian section of her first child and the subsequent pulmonary embolism and deep pelvic thrombosis. The FPA release was normal, whereas the fibrin polymerization was strongly decreased due to deleted Aα-segment with amino acid residues critical for fibrin polymerization. A functional fibrinogen concentration (< 0.25 g/L) and a fibrinogen antigen concentration (0.6 g/L) were decreased.

ACQUIRED DYSFIBRINOGENEMIAS

Disorders of fibrinogen structure and the resultant functions related to fibrin clot formation and enzymatic degradation can also be caused by environmental factors. This extremely heterogenous group of dysfibrinogenemias encompasses transient and persistent abnormalities resulted from medications (e.g. isotretinoin, glucocorticoid, antileukemic agents), autoantibodies, paraproteins[29] (typically in myeloma patients[30]), serious liver diseases[31] (hepatoma[32], chronic active hepatitis, cirrhosis[33], and isolated obstructive jaundice[34]). In most dysfibrinogenemias associated with liver disease or cancer a probable mechanism is increased sialylation of carbohydrate side chains in the Bβ and γ fibrinogen chains, which via increased negative charge impairs fibrin polymerization.

Growing evidence indicates that fibrin structure/function, reflected typically by reduced clot permeability and impaired fibrinolysis, is also unfavorably altered in patients following thromboembolic events including myocardial infarction[35], ischemic stroke[36], venous thromboembolism (VTE)[37]. This type of acquired dysfibrinogenemia is attributable to post-translational modifications of a fibrinogen molecule induced by several factors such as oxidative stress and elevated homocysteine levels[38]. The ε amino group of lysines in the fibrinogen molecule can be covalently modified by a highly reactive thioester, homocysteine thiolactone, present in small amounts in plasma. It has been reported that 10 lysines in the D– and αC-domains of fibrinogen can be homocysteinylated, which results in the formation of tightly-packed fibrin fibers not susceptible to enzymatic degradation, in part due to a decreased ability of modified fibrin to support t-PA-induced plasminogen activation[39].

Diabetes mellitus is a well--described example of dysfibrinogenemia associated with disease states. Altered fibrin structure in diabetes is largely attributed to glycation of fibrinogen molecules that may interfere with fibrin polymerization and cross-linking by FXIII[40].

Of note, cigarette smoking may also alter unfavorably fibrin clot structure and function in association with enhanced oxidative stress[41]. Furthermore, dysfibrinogenemia might be observed in inflammatory diseases such as chronic obstructive pulmonary disease[42] or rheumatoid arthritis[43], which is at least in part linked with augmented inflammatory state and elevated C-reactive protein levels. Acquired dysfibrinogenemia can be significantly improved by some medications, in particular aspirin[44] and statins[45]. However, the alterations in fibrinogen molecules reported in acquired dysfibrinogenemia rarely can prolong TT and usually are rather subtle.

SUMMARY

Congenital dysfibrinogenemias that result from mutations in one of the 3 fibrinogen chain genes on chromosome 4 are however asymptomatic in 50-60 % of the affected subjects and can be diagnosed incidentally. Typical results of coagulation tests found in dysfibrinogenemia are the combination of prolonged

TT, normal fibrinogen antigen, and a low functional level of fibrinogen. Dysfibrinogenemia could represent a rare thrombophilic factor that may cause arterial or venous thrombosis (<1% of thrombosis patients) as well as bleeding usually provoked by surgery, trauma or childbirth. In 25 % of patients, dysfibrinogenemia is associated with thrombotic events and 20% of cases with bleeding rarely life--threatening. Sometimes dysfibrinogenemia previously associated with thrombosis might be manifest as bleeding. Acquired dysfibrinogenemias are poorly described and involve alterations in fibrinogen structure induced by homocysteine, oxidative stress, glycation, leading to defective fibrin clot formation and its properties. This reversible abnormality rarely leads to prolonged TT.

Laboratory screening to exclude dysfibrinogenemia should be performed in selected patients with a history of bleeding or thrombosis and should include the measurement of TT besides routinely determined aPPT ad PT. Incidental detection of low fibrinogen levels (<1.5 g/L) using the most common von the Clauss method should lead to detailed evaluation of patients, including genotyping for fibrinogen mutations and family counseling. Inherited dysfibrinogenemia should be considered in patients with a personal and familial history of bleeding or thrombosis when other causes of these disorders have been excluded.

ACKNOWLEDGEMENTS

This work was supported by a grant of Jagiellonian University Medical College no K/ZDS/000565 (to A.U.).

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