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Congenital structural and functional fibrinogen disorders: a primer for internists

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Abstract

Congenital qualitative and quantitative fibrinogen disorders represent heterogeneous rare abnormalities caused by mutations in one of 3 genes encoding individual fibrinogen polypeptide chains, located on chromosome 4q28. It is estimated that congenital fibrinogen disorder accounts for 8% of rare coagulation factor deficiencies. Most of congenital fibrinogen disorders are suspected in individuals with bleeding tendency or coincidentally discovered, for instance prior to surgery. Fibrinogen disorders could be also found in patients with thrombotic events, impaired wound healing and recurrent spontaneous abortions. Afibrinogenemia manifests as mild to severe bleeding, while hypofibrinogenemia is often asymptomatic. Dysfibrinogenemia, a qualitative fibrinogen disorders, is associated with bleeding, thrombosis, or both, as well as no symptoms. Recent recommendations issued by the ISTH in 2018 do not encourage routine evaluation of thrombin time or other coagulation tests in patients suspected of congenital fibrinogen disorders, highlighting the value of fibrinogen antigen measurement and genetic analysis, added to the key finding, i.e. reduced fibrinogen concentration determined with a coagulometric assay. The current review summarizes practical issues in diagnostic work-up and clinical management of patients with afibrinogenemia, hypofibrinogenemia, dysfibrinogenemia and hypodysfibrinogenemia from a perspective of internists who may encounter patients with reduced fibrinogen concentration in everyday practice. Despite the fact that hematologists are in front line for the management of patients with bleeding tendency, internists should be aware of the clinical and laboratory findings in patients with inherited fibrinogen disorders including the risk of thromboembolism and management prior to invasive procedures.

Key words: fibrinogen, genetic mutation, dysfibrinogenemia, afibrinogenemia

Fibrinogen structure

Fibrinogen is a 340 kDa protein synthesized in the liver [1]. Its normal concentration in blood plasma is in the range of 1.5-4.0 g/L. The half-life of circulating fibrinogen is about 3-4 days. The fibrinogen molecule is a hexamer, made up of three pairs of homologous Aα, Bβ and γ polypeptide chains connected by disulfide bridges, that form a central E region composed by the N-terminal portions of all six chains and two terminal D regions containing the C-terminal fragments of the Bβ and γ chains [1]. The C-terminal fragments of the Aα chains form globular structures located near the central E region [1]. After cleavage of fibrinopeptides A and B under the action of thrombin, fibrin monomers are formed, which polymerize through the interaction of the D region with the E regions of subsequent monomers to form protofibrils and through their lateral aggregation, thick fibrin fibers are crosslinked in a reaction catalyzed by thrombin-activated factor XIII [1]. Fibrin, together with platelets and red blood cells, provide structural integrity to the hemostatic plug under physiological conditions and to the growing thrombus in thrombotic disorders.

The final fibrin clot has a highly heterogeneous structure, determined by genetic and to a much larger extent by environmental factors, which results in a large interindividual variability of clot architecture, thickness of fibers and their branching [2]. Lower fibrinogen concentrations are known to result in the formation of thicker fibrin fibers creating looser meshwork which are more susceptible to fibrinolysis and mechanical fragmentation, eventually leading to an increased risk of bleeding. On the other hand, irregular abnormal structure of fibrin, even at lower fibrinogen concentrations, could paradoxically increase thrombotic risk by impairing fibrin degradation by plasmin or facilitating clot fragmentation [2,3].

Congenital fibrinogen disorders

Genetic background

Congenital disorders of fibrinogen is a heterogeneous group of rare abnormalities most often caused by mutations in one of 3 separate genes encoding individual polypeptide chains, located on chromosome 4q28 in a cluster of about 50 kbp (*FGA*, *FGB* and *FGG*, respectively for chains Aα, Bβ and γ, but the order of genes from centromere to telomer is as follows: *FGB*, *FGA* and *FGG*) [4]. So far over 450 mutations in *FGA*, *FGB* and *FGG* genes have been registered, of which over 250 are symptomatic (www.geht.org). The most common mutations (50-80%) are

single-amino acid missense mutations. Other defects responsible for fibrinogen abnormalities include nonsense mutations, read frame changes through small deletions or insertions in the coding part of the gene (frameshift), splicing-site mutations and large deletions [4]. Less than 5% of cases are genetic variants located in the 3' and 5' untranslated regions of the genes [5]. Still, a few patients with severe fibrinogen deficiency have no identified genetic cause, and the use of next-generation sequencing (NGS) can help clarify genetic background of these disorders.

The causative mutations described so far result in either qualitative or quantitative fibrinogen disorders [4]. Quantitative disorders are traditionally divided into afibrinogenemia (complete absence of fibrinogen) and hypofibrinogenemia (proportionally reduced amount of functional and antigen) [4,6]. Afibrinogenemia are inherited in an autosomal recessive manner, while hypofibrinogenemia, dysfibrinogemia and hypodysfibrinogenemia are autosomal dominant [4]. Afibrinogenemia is due to homozygosity or compound heterozygosity of a null mutation [4]. It is estimated that quantitative congenital fibrinogen disorder accounts for 8% of rare coagulation factor deficiencies [5]. The prevalence of afibrinogenemia is estimated to be 1/1000,000 or more in some countries where marriages of closely related people are common, e.g. in Iran [4]. As hypofibrinogenemia are mainly caused by heterozygosity for fibrinogen gene mutation, they are much more frequent than afibrinogenemia.

Qualitative fibrinogen disorders include dysfibrinogenemia (normal amount of dysfunctional fibrinogen) and hypodysfibrinogenemia (decreased amount of dysfunctional fibrinogen). Almost all dysfibrinogenemias are caused by heterozygous missense mutations in *FGA* and *FGG* genes. Their prevalence is unknown as they are often asymptomatic [6]. In a recent systematic analysis of exome/genome data from about 140000 individuals of the genome databases, it has estimated that their prevalence is up to 0.3-1% [7]. Two hotspot mutations are particularly frequent, one affecting residue Arg35 in exon 2 of *FGA* and other affecting Arg301 in exon 8 of *FGG*. The mechanisms underlying clinical manifestations observed in qualitative congenital fibrinogen disorders involve abnormal formation of a fibrin clot associated with disturbed release of fibrinopeptides, delayed fibrin polymerization or defective cross-linking [4,8,9]. A single mutation altering a fibrinogen chain may result in significant changes in the tertiary and quaternary structure of the protein causing all the above disorders [4,8,9]. To date, about 30 different mutations causing hypodysfibrinogenemia have been identified (10 in the *FGA* gene, 5 in the *FGB* gene, and 15 in the *FGG* gene). Most of these fibrinogen mutations were inherited in an autosomal dominant manner [10]. Combined heterozygosity was found in

additional 7 patients with hypodysfibrinogenemia [10]. In patients with hypodysfibrinogenemia, the hypofibrinogenemic phenotype results from mutation affecting synthesis, assembly and secretion or leading to an increased fibrinogen clearance, while the dysfibrinogenemic phenotype results from impaired fibrin polymerization and abnormal binding of calcium ions or tissue plasminogen activator [10].

The first Polish case of dysfibrinogenemia, Fibrinogen Kraków associated with the Asn325Ile mutation in the fibrinogen γ chain and causing hypodysfibrinogenemia with thrombotic manifestation was described in 2009 [11]. Genetically characterized fibrinogens published for the first time in Polish patients are shown in Table 1 (the whole report – [12]).

Clinical manifestations

In patients with afibrinogenemia, umbilical stump bleeding in newborns is the typical first manifestation of the disease, observed in 85% of cases [13]. Bleeding in afibrinogenemia may also occur commonly as nosebleeds and less frequently cutaneous bleeding, gastrointestinal hemorrhage and genitourinary bleeding. Intracranial bleeding, often spontaneous, is the most common cause of death in patients with afibrinogenemia [13]. Intramuscular and hemarthrosis also occur in afibrinogenemia, usually less recurrently and less damaging than in severe hemophilia, even though severe arthropathies have also been reported in afibrinogenemia [5]. Three additional manifestations are considered specific for afibrinogenemia, namely spontaneous spleen rupture, impaired wound healing and the formation of painful bone cysts [14]. Afibrinogenemia in women is typically associated with spontaneous miscarriages in the first trimester of pregnancy [13]. Other pregnancy-related manifestations include pre- or postpartum hemorrhages, as well as placental abruption. Indeed, fibrinogen ensures placental integrity and is necessary for the development of blood vessels in its villi [13]. Over 50% of women with afibrinogenemia have prolonged heavy menstrual bleeding, requiring a hormonal treatment [13]. Paradoxically, patients with afibrinogenemia may have thromboembolic events associated with or without fibrinogen substitution treatment. Deep vein thrombosis and ischemic stroke are frequent but thromboses at unusual arterial and/or venous sites have also been reported [4,6,13,15].

Hypofibrinogenemia is often asymptomatic and diagnosed accidentally, especially when fibrinogen levels are higher than 1 g/L [6]. In the remaining patients, the bleeding phenotype predominates, depending on the fibrinogen level. Spontaneous bleeding events, such

as heavy periods, muscle hematomas, or gastrointestinal bleeding, occur in approximately 20% of patients with hypofibrinogenemia, especially when plasma fibrinogen concentrations does not exceed 0.5 g/L [13]. Hypofibrinogenemia are also associated with an increased risk of bleeding related to pregnancy, trauma or surgery [6]. It should be noted that in rare subtypes of hypofibrinogenemia, fibrinogen aggregates may accumulate in the endoplasmic reticulum of hepatocytes, leading to liver storage disease of varying severity [13].

Qualitative fibrinogen abnormalities are related to the reduced activity of normal amount of fibrinogen [8,10]. Clinical manifestations are heterogeneous. Approximately 55% of patients are asymptomatic, and about 50-60% of patients are diagnosed as part of work-up due to prolonged routine clotting times or reduced functional fibrinogen levels, e.g. before invasive procedures or during hospitalization [6]. Remaining patients can present a bleeding or/and a thrombotic phenotype. In a large cohort of patients with a median follow-up of 6 years, the overall incidence of major bleeding and thrombosis was 6 and 13.5 per 1000 adult patients/years respectively [8]. About 25% of patients with dysfibrinogenemia reported a mild bleeding tendency [8,13]. Pregnant women with dysfibrinogenemia can experience recurrent spontaneous miscarriages in the first trimester of pregnancy, placenta abruption, and postpartum thrombosis [13]. In a large patient cohort, approximately 20% of women experienced postpartum hemorrhage, and the risk was six times higher in women with previous bleeding phenotype [14]. For about 20% of cases, there is a tendency to venous and/or arterial thrombosis. The most classic example is the Dusart Fibrinogen, due to a single base change (C>T) in the A alpha-chain gene, resulting in the amino acid substitution Aα 554 Arg>Cys and consequently to the formation of very thin fibrin fibers with defective plasminogen binding [15]. Dysfibrinogemia is a rare cause of inherited thrombophilia (about 0.8%) [16] as compared to deficiencies of natural anticoagulants, but cannot be ignored [17,18]. There is evidence that dysfibrinogenemia can lead to a rare severe complication of pulmonary embolism such as thromboembolic pulmonary hypertension [19]. Therefore an extensive fibrinogen work-up is suggested by experts in patients with this type of pulmonary hypertension [14,20]. Pro-thrombotic mechanisms in dysfibrinogenemia may include reduced binding of thrombin to the abnormal fibrin network, abnormalities in fibrin polymerization with the formation of abnormal clot with tendency to fiber fragmentation and impaired fibrinolysis [13,21]. A correlation between genotype and phenotype is best documented for some dysfibrinogenemias, including thrombotic-related variants (described below) [5].

Hypodysfibrinogenemia is the most rarely reported congenital disorder of fibrinogen. It is associated with symptoms characteristic of both hypofibrinogenemia and dysfibrinogenemia [10]. In case of a discrepancy between reduced activity and reduced antigen fibrinogen levels, hypodysfibrinogenemia should be suspected [8,10]. Postpartum hemorrhage and menstrual disorders are particularly frequent, stressing out why this subtype of anomaly is most often described in symptomatic women [10,13]. The largest literature review published so far, reporting 51 patients diagnosed with hypodysfibrinogenemia, showed that the cut-off of 0.7 for the ratio of functional concentration of fibrinogen to its antigen level has a diagnostic sensitivity of 86% [10]. Interestingly, 22% of patients with hypodysfibrinogenemia did not show clinical manifestations at diagnosis, while 45% experienced at least one benign hemorrhagic event prior to diagnosis, 30% of which during pregnancy, puerperium and menstrual disorders [10]. Overall, 43% of patients in the studied cohort had at least one thromboembolic event with a predominance of venous thrombosis over arterial thrombosis (3:1) [10]. Spontaneous bleeding associated with fibrinogen abnormalities usually occurs at functional fibrinogen <0.7 g / L [9].

Classification of congenital fibrinogen disorders

The latest recommendations of the Research Standardization Committee at the International Society on Thrombosis and Haemostasis (ISTH) published in 2018 introduced a new classification of fibrinogen disorders and a modified diagnostic approach to patients with such a suspicion [22]. It has been suggested to classify congenital disorders in fibrinogen based on the clinical and biological (fibrinogen activity, antigen and genotype) phenotype [22].

Afibrinogenemia (**type 1** congenital fibrinogen disorder):

- asymptomatic or bleeding patients are classified as afibrinogenemia (**subtype 1A**),
- patients with concomitant thromboembolic events are classified as afibrinogenemia with phenotypic thrombosis (**subtype 1B),** even if accompanied by hemorrhagic episodes.

Type 2 includes patients with hypofibrinogenemia classified as:

- severe hypofibrinogenemia with a functional fibrinogen concentration <0.5 g/L (**subtype 2A**),
- moderate hypofibrinogenemia with a functional fibrinogen concentration of 0.5-0.9 g/L (**subtype 2B**),

- mild hypofibrinogenemia with a functional fibrinogen concentration from 1.0 g/L to the lower limit of the reference range (**2C subtype**),
- familial hypofibrinogenemia with accumulation of fibrinogen in the liver (fibrinogen storage disease), confirmed by histological examination (**2D subtype**).

Patients with dysfibrinogenemia (**type 3** congenital disorder) are distinguished by:

- asymptomatic dysfibrinogenemia or dysfibrinogenemia with bleeding tendencies or occasional thrombosis (**subtype 3A**), for which there is no clear association with the genotype,
- dysfibrinogenemia associated with thrombosis (**subtype 3B**) found in patients carrying a known mutation increasing the risk of thrombosis (Fibrinogen Dusart, Caracas V, Ijmuiden, New York I, Nijmegen, Melun and Naples in a homozygous form) or in patients with venous thrombosis or at an early age with a positive family history of thrombosis in 1st degree relatives (of the same genotype) with no other known cause of thrombophilia.

The last group of congenital fibrinogen disorders (**type 4**) includes patients with hypodysfibrinogenemia classified as:

- severe hypodysfibrinogenemia with fibrinogen antigen <0.5 g/L (**subtype 4A**),
- moderate hypodysfibrinogenemia with fibrinogen antigen levels between 0.5 and 0.9 g/L (**subtype 4B**),
- mild hypodysfibrinogenemia with fibrinogen antigen levels from 1.0 g/L to a lower limit of the reference range (**4C subtype**).

This recent classification [22] did not include patients with an inherited fibrinogen Aα chain mutation that causes amyloidosis and fibrinogen chain deposition in the kidneys because this fibrinogen variant does not affect routine screening coagulation tests [23].

For all patients, regardless of the type of the fibrinogen mutation found, it is important to note:

- age at diagnosis,

- the circumstances in which the disease was diagnosed,

- similar abnormalities or symptoms in the family,

- the type of clinical manifestation (hemorrhagic, with major life-threatening bleeding, with recurrent thromboembolic events or with the need for fibrinogen concentrates) [18].

Diagnostic work-up of congenital fibrinogen disorders

Diagnosis of congenital fibrinogen disorders is difficult due to the availability of various analytical methods and reagents to assess the function of blood coagulation and the large number of mutations in the three fibrinogen genes leading to different protein concentration [4,16]. Traditionally, fibrinogen is the only coagulation factor whose potency is expressed in units of concentration (most commonly in clinical practice as g/L), rather than in activity units like other coagulation factors**.** The measurements of fibrinogen concentrations are standardized. Decreased fibrinogen concentrations should lead to a suspicion of congenital fibrinogen disorders and a further diagnostic evaluation should be performed. Of note, a concentration of fibrinogen, as an acute phase protein, increases in response to inflammatory diseases, infections, nephrotic syndrome, during pregnancy, during the use of oral hormonal contraceptives, or after surgical interventions, making diagnosis even more challenging and requiring sometimes repeated measurements [1,4].

Coagulation tests most commonly used in the diagnosis of congenital fibrinogen disorders include:

- prothrombin time (PT), also automatically expressed in most laboratories as international normalized ratio (INR),

- activated partial thromboplastin time (APTT),

- thrombin time (TT),

- assessment of fibrinogen concentration by the von Clauss method [24].

Even a single measurement indicating plasma fibrinogen concentration <1.5 g/L should lead to a more extensive diagnostic work-up and, if necessary, genetic testing. The TT assay, which is poorly standardized, has the highest diagnostic sensitivity, although, like PT and APTT, the TT assay has low specificity [25]. The measurement of PT, APTT, functional concentration of fibrinogen, and the level of its antigen should constitute the first stage of diagnostic evaluation in a patient suspected of congenital fibrinogen disorders [22]. Determination of the functional

concentration of fibrinogen by the von Clauss method is based on the measurement of the coagulation time of poor platelet plasma (by mechanical or optical methods) after activation with high concentration thrombin [26]. Antigen levels are usually measured using specific antibodies with detection by immunodiffusion techniques, immunonephelometry or immunoturbidimetry [26].

If the measurement of fibrinogen antigen is not available in a given laboratory, the method of choice should be the determination of fibrinogen concentration based on PT (PT-derived fibrinogen assay) in order to calculate the ratio of fibrinogen concentration measured by the von Clauss method [26]. PT-derived fibrinogen is an indirect measurement in which the concentration of functional fibrinogen can be estimated on the basis of changes in the optical density of plasma, where the difference in optical density is proportional to the concentration of fibrinogen compared to subsequent dilutions of the standard with known concentration of this protein [26]. Compared to the von Clauss assay, this method is sensitive to changes in plasma optical density associated with slower fibrinopeptide release and formation of thicker fibrin fibers [26]. Therefore, in patients with dysfibrinogenemia, the PT-based measurement of fibrinogen concentrations overestimates its actual concentration five times compared to the von Clauss assay and thus correlates with protein levels measured by immunological methods [26]. It is a common practice to use a cut-off of <0.7 for the ratio of fibrinogen measured by the von Clauss assay and the antigen or the PT-based method in the diagnosis of dysfibrinogenemia [19]. It should be noted that some variants, e.g. fibrinogen Longmont (*FGB* Arg166Cys) or fibrinogen Bordeaux (*FGA* Arg439Cys), have an apparent decrease in fibrinogen concentration measured using the PT based method compared to the von Clauss assay [22,27,28].

TT and reptilase time (RT) in the presence of congenital fibrinogen disorders are often prolonged, but according to the current ISTH guidelines [22] they should be considered only as additional tests in patients, due to the limited diagnostic value. Indeed, even though TT is commonly used by hematologists as a dysfibrinogenemia screening test, results in the reference range (with prolonged RT), as well as prolonged TT, still require measurement of functional fibrinogen and its antigen level.

Regardless of the diagnostic algorithm, in order to establish the definitive diagnosis of inherited fibrinogen disorders, a detailed analysis of the genes encoding individual fibrinogen chains is necessary, in association with screening of this abnormalities in relatives and assessment of the relationship between the genotype and the clinical phenotype [22]. It is recommended that in quantitative fibrinogen disorders, genetic analysis should start by sequencing *FGA* gene (exon

4 and 5), because they often contain mutations associated with protein function loss [29]. The next step should be the analysis of less commonly mutated exons (*FGA* - exon 2, *FGB* - exons 2 and 6 and *FGG* - exons 6 and 8) and, if necessary, sequencing of the remaining exons [29]. In dysfibrinogenemia, the first stage of the diagnostic work-up should be the screening of exon 2 of the *FGA* gene and exon 8 of the *FGG* gene [29]. Next, exon 5 in *FGA*, exon 2 in *FGB* and exons 3 and 5 in *FGG* should be assessed [29]. However, nowadays next-generation sequencing (e.g. whole exome sequencing) is being more cost-effective in the identification of a causative mutation in rare disease. Standard Sanger PCR are still useful to confirm the molecular anomaly or for familial studies.

Management of bleeding in congenital fibrinogen disorders

Treatment of a- or hypofibrinogenemia and sometimes dysfibrinogenemia is to provide adequate concentrations of functional fibrinogen for proper hemostasis by using freshly frozen plasma (FFP), cryoprecipitate or plasma-derived fibrinogen concentrate. The last is the best option [5,14]. Cryoprecipitate and FFP are associated with infusion-related adverse reactions, including the risk of fluid overload and transfusion-related acute lung injury (TRALI) as a potentially fatal adverse event [30]. In addition, the use of FFP and cryoprecipitate is associated with the supply of large amounts of other proteins as fibronectin, von Willebrand factor, factor VIII, factor XIII, and macroglobulin [30]. Finally, both require thawing, which delays the infusion of the first dose. Clinical studies have shown that the risk of transmitting a pathogen by administering fibrinogen concentrate is negligible [30]. Fibrinogen concentrate infusion can be complicated by allergic reactions. The formation of antibodies against this protein have been reported, but without inhibitory effects [31].

The patients who require fibrinogen supplementation should be treated by hematologists trained in therapy of bleeding disorders. To summarize the key concepts for internal medicine specialists, who may encounter such patients occasionally, it should be highlighted that the therapeutic goal based on expert opinions and observational studies is to achieve a functional fibrinogen concentration (coagulometric method) of 1-1.5 g/L. The value of 1 g/L is currently considered the minimal concentration of fibrinogen to maintain the asymptomatic state in most patients, based on publication from the European Network of Rare Hemorrhagic Diatheses [32], however some experts suggest a lower target concentration of fibrinogen, i.e. 0.5-1 g/L. Fibrinogen is administrated either “on demand” in case of acute bleeding or surgery either “as

prophylaxis" in patients with afibrinogenemia or severe hypofibrinogenemia to prevent occurrence of bleeding. Long-term prophylaxis is recommended in patients with afibrinogenemia suffering from major recurrent bleeding, but such strategy can also be considered in primary prophylaxis (i.e. before occurrence of first bleeding). Usual infusions strategies, according to the type of product, are indicated below:

On demand:

- fibrinogen concentrate 50-100 mg / kg

- cryoprecipitate 15-20 ml / kg

- FFP 15-30 ml / kg [5].

On prophylaxis:

- fibrinogen concentrate 30-100 mg / kg bw every week

- cryoprecipitate 1 unit 3 times a week or 3 units every 7-10 days [5].

The final dosage should be adjusted individually depending on the frequency of bleeding and its severity. Isolated cases of unsatisfactory hemostasis with recurrent bleeding at fibrinogen> 1 g / L have been reported [30]. Increased fibrinogen clearance is seen during major bleeding, which requires increased fibrinogen concentrate dosage with close monitoring. In the case of acute bleeding, it is recommended to administer fibrinogen based at least on daily monitoring [30]. Tranexamic acid can also be administered in the event of minor bleeding or minor surgery planned in patients with hypofibrinogenemia or dysfibrinogenemia with a bleeding phenotype [14]. In women with heavy menstrual bleeding, especially with hypofibrinogenemia, hormonal agents should be considered in addition to oral tranexamic acid during menstrual bleeding.

Management of pregnant women

Pregnancy is a high-risk clinical situation in women with congenital fibrinogen disorders, especially in afibrinogenemia. A multidisciplinary approach including obstetrician, hematologist and anesthetist, preferably in a hemophilia center, is of key importance, and such women should be referred to it at the first contact with an internist. In women with afibrinogenemia or severe hypofibrinogenemia fibrinogen infusion should be started as soon as

possible [33]. Increased fibrinogen clearance is observed in the third trimester of pregnancy, requiring an increase in the dosage of fibrinogen concentrate with a close monitoring of peak and trough fibrinogen levels [34]. In women with dysfibrinogenemia and history of recurrent miscarriages, fibrinogen supplementation could be considered to achieve a functional concentration of fibrinogen of around 1 g/L [30]. However, such strategy does not guarantee favorable outcomes and the risk of miscarriage, especially in the first trimester of pregnancy, remains significant [30]. There is no data showing that after normalization of fibrinogen concentration in dysfibrinogenemia, hemostasis is still defective. Post-partum hemorrhage is a frequent complication and should be monitored closely. An increased post-partum thrombotic risk has been reported. An appropriate thromboprophylaxis should be considered in selected women following childbirth [30].

Management of thrombosis

Occurrence of thrombosis in afibrinogenemia is a clinical conundrum. One hypothesis is that the generation of thrombin in a hematoma or during surgery or during pregnancy, without the antithrombin action of fibrin (i.e acting as a trap for circulating thrombin) can lead to strong platelet activation and aggregation stimulated by thrombin and endothelial cell injury, which in turn promotes thrombus formation and thromboembolic events in both the venous and arterial systems [35]. Thrombosis in such patients requires simultaneous supplementation of fibrinogen and administration of anticoagulants, most often heparins, with close clinical supervision and laboratory monitoring. Oral direct thrombin inhibitors and antiplatelet agents, in particular vorapaxar, a protease-activated receptor 1 antagonist, might be considered in afibrinogenemic patients with recurrent arterial thromboses, however in most countries these agents are unavailable and their safety remains controversial [36]. Besides the few thrombotic-related dysfibrinogenemic variants, all dysfibrinogenemia can contribute to an increased thrombotic risk. Heparins, precisely low-molecular-weight heparins, e,g. enoxaparin, are the drug of choice in treatment of thrombosis in such patients as vitamin K antagonists cannot be reliably monitored with INR. The chromogenic assay of factor X could be used to determine the correct INR value on warfarin in patients with dysfibrinogenemia, In whom the INR cannot be accurately determined due to interference with the fibrin endpoint in the INR assays [37]. A duration of anticoagulation depends on the type of thrombosis, the familial history and the overall patient's phenotype. In view of this potential thrombotic risk, thromboprophylaxis with

heparins should be administrated in all clinical settings with an increased thrombotic risk [16], in particular during pregnancy and postpartum [38].

Key points for internists

Due to the rarity of congenital fibrinogen disorders, internists are often not aware of such a condition. Subjects in whom reduced fibrinogen concentrations are measured should be referred to hematologists for further work-up regardless of the presence or absence of any clinical manifestations to establish a definite diagnosis. Even if patients with severe fibrinogen disorders are treated in hemophilia centers, internists should recognize signs and symptoms that should require an emergency treatment as well as refer subjects and their relatives suspected of this type of disorders to specialized centers. Internists and general practitioners should endorse the management in cooperation with the hematologist and treat other diseases, e.g. influenza, bacterial infections in patients with congenital fibrinogen disorders being knowledgeable about thrombotic or bleeding risk. In terms of the management of pain, internists should be aware of the fact that nonsteroidal anti-inflammatory drugs inhibiting platelet aggregation, e.g. aspirin should be avoided in patients with congenital fibrinogen disorders and a bleeding phenotype [39]. Thienopirydines should not be used in such patients either. In asymptomatic fibrinogen disorders, the use of antiplatelet agents following acute myocardial infarction or stroke is initiated and any changes in the therapy should be discussed with a cardiologist and hematologist [40]. On the other hand, thrombosis in patients with congenital fibrinogen disorders, in particular some dysfibrinogenemias, should be effectively managed and reduced fibrinogen concentrations should not lead to a false assumption that patients are at high bleeding risk and anticoagulation should be stopped prematurely. Such decisions should be discussed with specialists to avoid recurrent thromboembolism. Some general aspects of management and recommendation for internists who take care of patients with congenital fibrinogen disorders are presented in Table 2.

Conclusions

Congenital qualitative and quantitative fibrinogen disorders are rare. A widely available and cheap determination of plasma fibrinogen concentration using a coagulation assay should be considered in patients with bleeding including persistent minor bleeds and heavy menses, in particular when there is a positive family history. Fibrinogen level measurement should be also

considered in pregnancy complications and thrombosis without clear risk factors. A patient suspected of having afibrinogenemia, hypofibrinogenemia or dysfibrinogenemia, with lower fibrinogen concentrations (without obvious acquired cause e.g. disseminated intravascular coagulation [DIC], or massive acute thrombosis), should be referred to a specialist hematology center for further diagnostic work-up including genetic evaluation and family counselling. Proper management is effective in most patients who manifest bleeding related to fibrinogen disorders, therefore search for this abnormality should be encouraged. In Poland like in many lower-income countries, congenital fibrinogen disorders are underdiagnosed and sparsely reported. Efforts to change this situation should be started from increased awareness of afibrinogenemia, hypofibrinogenemia or dysfibrinogenemia among general practitioners and internists.

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Table 1. Congenital fibrinogen disorders genetically characterized for the first time in Polish patients.

fibrinogen	**Classification ISTH**	**Gene**	**Mutation**	**Sex, age at diagnosis**	**Functional fibrinogen concentration / fibrinogen antigen level (in g / L)**		**TT, sec**	**Clinical symptoms**	**Bleeding / thrombosis in the family**
Belchatow	2B. moderate hypofibrinogenemia	*FGG*	IVS1+5 G>C, c.78+G>C	Woman, 33 years old	0.94/1.2		31.8	2 postpartum hemorrhages, 2 miscarriages	YES
Cracow	4C. mild hypodysfibrinogenemia	*FGG*	c.1052A>T, p.Asn325Ile	Woman, 21 years old	0.62/1.16		21.5	Accidental diagnosis during the first pregnancy; at the age of 16, appendectomy complicated by deep vein thrombosis	YES
Cracow III	3A. dysfibrynogenemia	*FGG*	c.124G>A, p.Gly16Ser	Woman, 44 years old	2.1/2.29		22.5	Bleeding after delivery and tooth extraction	NO
Poznań	2C. mild hypofibrinogenemia	*FGG*	c.331 A>T, p.Lys111X	Man, 25 years old	1.0/1.12		21.1	32-hour bleeding after tooth extraction, bleeding from minor wounds	YES

								and nose, easy bruising	
Poznan II	3A. dysfibrynogenemia	*FGG*	del 177bp	Woman, 47 years old	1.81/2.6		19.1	Spontaneous miscarriage at 33 years complicated by vaginal bleeding, prolonged menstrual bleeding, easy bruising	YES
Zakopane	2B. moderate hypofibrinogenemia	*FGG*	IVS2-2 A>C, c.124-2A>C	Male, 23 years old	0.93/1.2		26.3	Detected accidentally	YES

Abbreviations: APTT - partial thromboplastin time after activation, PT - prothrombin time, TT - thrombin time

Table 2. General considerations for internists managing patients with fibrinogen disorders

In afibrinogenemia and severe hypofibrinogenemia, all new symptoms should be considered as bleeding and treated accordingly until additional investigations are performed
In afibrinogenemia and severe bleeding, all invasive procedure (including venipuncture) should be avoided and performed only upon approval of hematologist
Nonsteroidal anti-inflammatory drugs should be avoided in patients with a bleeding phenotype and paracetamol should be preferably used.
Hormonal contraception should be suggested in afibrinogenemic women and severe hypofibrinogenemic women with heavy menses
Annual visit to a hemophilia center should be organized for all patients with fibrinogen disorders
Thromboprophylaxis should be considered in patients with dysfibrinogenemia according to recommendations of a given hemophilia center
Surgical procedure and pregnancy management should be performed under the guidance of specialized centers dealing with bleeding disorders