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Review

Guideline for diagnosis and management of congenital dysfibrinogenemia

Jie Yan [a,b], Lin Liao [a,b,c], Donghong Deng [d], Weijie Zhou [a,b,c,e], Peng Cheng [d], Liqun Xiang [a,b], Meiling Luo [a,b], Faquan Lin [a,b,c,*]

[a] Department of Clinical Laboratory, the First Affiliated Hospital of Guangxi Medical University, Nanning, Guangxi, China
[b] Key Laboratory of Clinical Laboratory Medicine of Guangxi, Department of Education, China
[c] Guangxi Medical Doctor Association-Laboratory Medicine, China
[d] Department of Hematology, the First Affiliated Hospital of Guangxi Medical University, Nanning, Guangxi, China
[e] Clinical Laboratory, Baise People's Hospital, Baise, China

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ABSTRACT

Introduction: Congenital dysfibrinogenemia (CD) is characterized by dysfunction induced by an abnormal fibrinogen molecule structure that results in blood coagulation dysfunction. The clinical manifestations of CD patients are asymptomatic, bleeding and thrombosis. The majority of patient are asymptomatic. However, the single fibrinogen detection method is easy to cause missed diagnosis or misdiagnosis of CD patients. The treatment strategies of CD patients with different clinical manifestations are also different.

Methods: Combing the existing experimental diagnosis technology, literature and our research results, a simple and practical CD diagnostic criteria was proposed. And based on the relevant literature and existing treatment guidelines, more comprehensive treatment recommendations are summarized.

Results: In this new criteria, combination Clauss method and PT derived method was proposed to detect fibrinogen and its ratio was used to diagnose for CD. Diagnosis also needs to be combined the clinical manifestations, family investigation and genetic testing. According to different clinical manifestation (bleeding, thrombosis or asymptomatic), treatment methods and strategies are different. The treatment of CD patients should consider the patient's personal and family history of bleeding or thrombosis. Treatment of thrombosis and pregnancy may be more challenging. The risk of bleeding and thrombosis should be evaluated and balanced at all times during clinical treatment. These detailed treatment recommendations can provide reference for patients with different clinical manifestations of CD.

Conclusions: The new CD diagnosis criteria and comprehensive treatment recommendations can effectively improve the diagnosis and treatment of CD.

1. Introduction

Congenital fibrinogen deficiencies can be divided into two clinical categories. Type I refers to quantitative (afibrinogenemia and hypofibrinogenemia) and Type II is the quality defect (dysfibrinogenemia) [1]. Congenital dysfibrinogenemia (CD) is characterized by dysfunction induced by an abnormal fibrinogen molecule structure that results in blood coagulation dysfunction, which is often characterized by fibrinogen activity decreased and antigen normal or elevated, and most are autosomal dominant inheritance [2]. There are no specific statistics on the prevalence of the disease in the population because most asymptomatic patients with CD are missed or unreported [3]. At present, more and more patients with CD are being found, especially many asymptomatic patients who are diagnosed with abnormal coagulation function before surgery. The World Hemophilia Federation 2017 Hemorrhagic Diseases Survey report: in the proportion of hemorrhagic diseases in 113 countries, fibrinogen deficiency (including Type I and II defects) accounted for 6 % of the hemorrhagic diseases except hemophilia A, Hemophilia B and von Willebrand disease, and China is as high as 37 %. With the fast-growing of molecular and gene technology, a deeper understanding of the fibrinogen gene and its protein function will help to understand the molecular pathogenesis of CD and provide help for its diagnosis and clinical treatment.

Clinical diagnosis is based on the laboratory tests, clinical manifestation or radiological imaging [4]. Here in this paper, according to the existing experimental diagnosis technology, literature and combining

* Corresponding author at: Department of Clinical Laboratory, the First Affiliated Hospital of Guangxi Medical University, Nanning 530021, Guangxi, China.
E-mail address: fqlin1998@163.com (F. Lin).

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with our research results, a simple and practical CD diagnosis criteria was proposed. And the relevant treatment recommendations for different clinical manifestations of CD patients (included bleeding, thrombosis or asymptomatic) were also summarized.

2. Structure and physiological function of fibrinogen

Fibrinogen is a symmetric dimer composed of two identical subunits, each of which containing three highly homologous polypeptide chains (α, β, γ). The three peptide chains of fibrinogen are encoded by three homologous genes (FGA, FGB and FGG) respectively. Peptide chains and subunits are linked to each other by disulfide bonds, with about 28 or 29 disulfide bonds throughout the molecule. Each fibrinogen molecule has one E region and two D regions [5]. The E region is composed of the amino terminus (n-terminus) of six polypeptide chains, and the C-terminal folding of Aα also participates in the formation of the E region structure. D region is composed of the carboxyl terminus (C-terminus) of the Bβ and γ chains. The D region was connected to the two E regions by Aα, Bβ and γ peptide chains respectively. The precursor proteins of the three peptide chains are synthesized by the ribosome in the cell firstly. Then, the processing of signal peptide removal, hydrophobic reaction and disulfide bond formation of the translated protein are carried out in the endoplasmic reticulum and Golgi apparatus. Finally, after glycosylation, phosphorylation and other modifications, the protein is secreted out of the cell. Its circulation has a half-life of 3–4 days [6].

The main physiological function of fibrinogen in vivo is to participate in coagulation and hemostasis. The conversion of fibrinogen to fibrin is divided into the following three steps: (1) fibrinopeptide A and fibrinopeptide B are released after the specific hydrolysis of the peptide bond by thrombin to form fibrin monomer [7]. After the release of fibrin peptide, the "A" site composed of glycine, proline and arginine complements the "A" site in the D region of the adjacent fibrinogen molecule to form "A-A" binding. The "A" site was mainly composed of glycine 329, aspartic 330 and aspartic 364 of the γ chain. The "B" site in the E region is composed of glycine-histidine-arginine-proline. The "B" site is complementary to the "B" site of the adjacent fibrinogen molecule, forming a "B-B" binding [8]. Specific location of site "B" has not been clarified yet [9]. (2) fibrin monomers spontaneously polymerize to form fibrin primordium through E-D binding and D-D crosslinking. The binding of E region and D region refers to the covalent polymerization of "A" site and "B" site in E region, and the complementary "A" site and "B" site in D region. D-D crosslinking refers to the mutual polymerization between two adjacent fibrinogen D region γ chains. There are mainly four amino acid residues involved in D-D surface contact. The arginine at 275 on the γ chain of the first molecule binds to tyrosine at 280 on the γ chain of the second fibrinogen molecule, which binds to ser300 on the γ chain of the first molecule. E-d binding and D-D crosslinking make the fibrin monomer polymerize to form overlapping primary fibrin fibers [10]. (3) with the participation of coagulation factor FXIII and Ca^{2+}, fibrin primary fibers cross-linked to form a stable fibrin network structure, which surrounded blood cells to form hemostatic thrombus. FXIII can catalyze the covalent cross-linking of adjacent gamma chains to produce stable fibrin clot structure [11].

For the CD, mutation in the gene that codes for three peptide chains (Aα, Bβ and γ) cause abnormality in the function of fibrinogen without affecting the amount of fibrinogen. The abnormality of fibrinogen function is characterized by fibrin peptide release disorder or delay, fibrin monomer polymerization abnormality, fibrin monomer cross-linking abnormality and fibrin fibrinolysis abnormality and so on. Such as Aα(11Glu → Gly), Glutamate at position 11 of the Aα chain is replaced by glycine and mutation causes delay in the release of fibrinopeptide A [12]. Aα chain 16Arg-l7Gly is the site of thrombin cleavage and Aα chain (16Arg → His or Cys) is one of the most commonly reported mutation sites, which resulte in abnormal thrombin binding sites and delayed release of fibrin peptide A [13,14]. The three important amino acids of D-D crosslinking are γArg275-γTyr280-γSer300 [15], and any change of amino acids can cause abnormal polymerization of fibrin monomer. γArg275His or Arg275Cys is another hot mutation site. Mutation in γArg275His or Arg275Cys weaken D-D bridging and affect the linear connection of fibrin monomers, resulting in delayed polymerization and clot formation.

3. The diagnosis of congenital dysfibrinogenemia

3.1. Laboratory tests

3.1.1. Thrombin time

Thrombin time (TT) assay is the fibrin clot formation mediated by thrombin immediately after the addition of "standardized" thrombin in the plasma to be tested [16]. TT is used to evaluate the conversion of fibrinogen to fibrin and reflect the rate of fibrin clot formation [17]. Fibrin monomer is formed after the cleavage of fibrin peptide A and fibrin peptide B in the fibrinogen, and the fibrin monomer is polymerized vertically and horizontally to form fibrin clot. In CD patients, fibrinogen molecular structure abnormalities and functional defects can inhibit the cleavage of fibrin peptide A and/or B, and then delay the polymerization of fibrin monomer. Almost all patients diagnosed with CD by Lin et al. had prolonged TT [18–23]. Casini et al. investigated 101CD patients and found that 87.6 % of the patients had prolonged TT. It can be seen that TT is a sensitive indicator for the diagnosis of CD. Therefore, TT can be used clinically to detect hypofibrinogenemia, dysfibrinogenemia or thrombin inhibitor (such as heparin) [17]. However, the specificity of the thrombin time for CD is not well good. Other factors can also lead to prolonged TT, like heparin or hirudin, heparin-like substances and fibrin degradation product.

3.1.2. Prothrombin time and activated partial thromboplastin time

The detection procedure of prothrombin time (PT) is to add excessive tissue thrombin (a mixture of TF, lipids and calcium chloride) to the plasma. Then the prothrombin becomes thrombin, which in turn causes the fibrinogen to become fibrin. So, PT is often used to assess exogenous and common clotting pathways, and is therefore affected by coagulation factor II (FII), V (FV), VII (FVII), X (FX) activity and fibrinogen deficiency [24]. The absence of one or more clotting factors in the clotting pathway, or the presence of inhibitors of these factors, can lead to prolonged PT [25]. In addition, liver failure, vitamin K deficiency, heparin (high doses), high levels of antiphospholipid antibodies and fibrin degradation product also lead to prolonged PT [17]. In the clinic, PT and international normalized ratio (INR) are often used to monitor vitamin K antagonists (like warfarin) anticoagulant therapy [24]. In the anticoagulant plasma, sufficient amount of active contact factor activator, part of thromboplastin and appropriate amount of calcium ions were added. The time required from the addition of calcium ions to plasma coagulation is called activated partial thromboplastin time (APTT). The causes of prolongation of the APTT included deficiencies of factors XII(FXII), XI(FXI), IX(FIX), VIII(FVIII), X(FX), II (prothrombin) and/or I (fibrinogen), high-molecular weight kininogen, fibrin degradation products, lupus anticoagulant (high levels), heparin and so on. APTT is often used to monitor heparin therapy and as a screening test for haemophilia in the clinic [17,26]. The test of PT or APTT didn't need to add extra thrombin. They will converge into the common pathway, which is to make the production of thrombin through prothrombin and the conversion of fibrinogen to fibrin by thrombin [27]. PT and APTT are commonly screening experiment for the absence of coagulation factors involved in exogenous or endogenous pathways.

CD is characterized with fibrinogen dysfunction but with the normal level of fibrinogen. The PT and APTT of CD patients are in the normal reference range generally [28]. Zhou et al. reported that 102CD patients all displayed normal APTT and PT [29], and other studies also have reported CD patients were with normal APTT and PT [18,19,30]. PT and APTT have low sensitivity and specificity in diagnosing fibrinogen dysfunction. The abnormal of PT and APTT are of little help in

diagnosing CD. At present, the reasons for the normal of PT and APTT in CD patients may be as follows: (1) Normal PT and APTT may be related with the assay conditions. In the detection process of PT and APTT, adding Ca^{2+} can enhance fibrin polymerization. Another possibility is that the amount of thrombin produced in PT and APTT responses is relatively small, and that about half of the plasma fibrinogen in heterozygous missense mutations of CD patients is considered normal, so a relatively small amount of thrombin may cause PT and APTT responses similar to normal plasma [31]. (2) At present, the detection principle of automatic coagulation analyzer is mainly based on transmission turbidimetry. PT and APTT depend on the process of conversion of fibrinogen to fibrin, but pay attention only to the initiation of this process, not to its speed or total extent [26]. Self-polymerization of fibrin monomer can form turbidity and the change of absorbance caused by turbidity can be detected by coagulation analyzer. Therefore, the instrument show that PT and APTT are normal.

3.1.3. Fibrinogen Clauss method

Fibrinogen assays are useful for the diagnosis of hypofibrinogenemia, dysfibrinogenemia, disseminated intravascular coagulation, primary fibrinolysis and other clinical conditions [17]. The method of fibrinogen assays included numerous methods, for example thrombin method, PT-derived method and immunological method, nephelometric and so on [32].

At present, most clinical laboratories used thrombin method recommended by WHO to detect fibrinogen. Thrombin method, also known as Clauss assays, is the method that high concentrations of thrombin was added to the dilution of patient's plasma, the plasma is immediately coagulative, and the coagulation time is negatively correlated with the fibrinogen concentration, and then the fibrinogen concentration is obtained from the standard curve of the fibrinogen reference plasma determination of the international standard. The Clauss method also can measures the rate of clot formation [33]. The fibrinogen activity is most commonly determined by the Clauss method and activity is based on the measurement of fibrin polymerization function [33]. Fibrinogen dysfunction influence fibrin polymerization function. So, CD are characterized with reduced fibrinogen activity [28]. Most modern laboratories used automated clotting analyzer matched commercial kit. The results of fibrinogen can be calculated automatically by the software from the computer [34]. It is worth noting that each laboratory should establish its own normal range. In order to ensure the reliability and accuracy of the determination results, the fibrin reference plasma must be measured in parallel with the plasma to be tested.

In addition, clinical drugs may interfere with Clauss fibrinogen assays, resulting in reduced fibrinogen fallibility [35]. For example, some common thrombin inhibitors include bivalirudin, lepirudin, argatroban and so on. A multicenter study had found that the INR, APTT and TT prolonged with the increase of the concentration of dargebyn, but the result of fibrinogen may be either unaffected or lower [36]. Another study demonstrated the Clauss fibrinogen assay (turbidmetric) was affected by bivalirudin and fibrinogen concentration was falsely reduced during bivalirudin anticoagulation [37]. Zhang et al found that fibrinogen Clauss reagent, especially with low concentration of thrombin, was greatly affected by argatroban and therefore the low fibrinogen concentration may be got [35]. However, argatroban had no influences on immunoassay.

3.1.4. Fibrinogen PT-derived method

PT-derived method is based on the derivation of the PT reaction curve to indirectly measure the concentration of fibrinogen. Firstly, the primary function equation of the automatic coagulation curve of PT is obtained. The reaction absorbance difference is obtained through the curve, and then the difference is substituted into the equation to calculate the concentration of fibrinogen [38]. That is, when all fibrinogen in plasma is converted into fibrin, the change in turbidity is proportional to the fibrinogen content so that fibrinogen can be calculated. What's more, PT-derived method didn't require extra reagent. It had been proven to be quick, economical and easily available to laboratories with suitable instruments [39]. Guvenet al. wanted to study the effectiveness of PT-derived method and found that the PT-derived method can be used alone especially in patients with an INR < 1.2 [40]. There may exist some controversy that if the PT-derived method can be applied as a routine screening method. This may be due to concerns about the correlation between PT-derived method and immunoassay. However, there have been studies exploring the two methods. It had suggested that PT-derived method can be used as an alternative if immunoassays for fibrinogen antigen are unavailable in laboratory diagnosis of fibrinogen deficiency [41]. And some studies supported that the PT-derived method correlated well with the fibrinogen antigen concentration determined with immunoassays [23,42,43]. There was study thought that PT-derived method was accurate and precise for most routine purposes [44].

CD patients are with normal or increased antigen levels associated with reduced functional activity. In the clinical work, PT-derived method may not be suitable for use alone, which may lead to miss diagnosis. It should be best to combine with Clauss method for screening or diagnosis of dysfibrinogenemia. This will greatly improve the diagnosis of CD.

3.2. The fibrinogen PT-derived method /Clauss method ratio

Previous studies have reported the fibrinogen activity–antigen ratio may be as screening or diagnostic indicator for CD patients [1,45]. But the sensitivity and specificity values of this ratio are not well known [33]. Shapiro et al. used automated clotting analyzer with matching reagents from different manufacturers to detect fibrinogen, and found that 35 patients with CD showed similar laboratory features irrespective of genotype and had significantly reduced result by Clauss method while the result of PT derived method was normal [3]. Miesbach et al. reported that the results of fibrinogen detected by PT derived method in 27 patients with CD was about 5 times higher than that of Clauss method, independent of reagents and instruments used [43]. A previous study that included 81 healthy controls and 73CD patients to explore the ratio of fibrinogen Clauss method combined with the PT-derived method. The results showed the levels of fibrinogen detected by Clauss method and PT-derived group were 3.56 ± 0.70, 3.95 ± 0.66 g/L respectively in the normal control group. In the group of CD patients, the levels of fibrinogen detected by Clauss method and PT-derived group were 0.62 ± 0.19 and 3.70 ± 0.88 g/L, respectively [23]. It is obvious that the fibrinogen detected by PT-derived method was significantly higher than Clauss method [39]. In particular, receiver operating characteristic (ROC) curve analysis had revealed that when the fibrinogen antigen/activity ratio (PT-derived method/Clauss method) was >1.43, both the sensitivity and specificity of CD diagnosis were 100 % [20]. These results indicated that the combination of Clauss method and PT-derived method for the determination of fibrinogen is a specific and sensitive test for CD diagnosis. Casini et al. recommended that if antigenic measurement is not possible, as second choice method, the PT-derived method /Clauss ratio >1.43 can be used to diagnose for CD [46].

3.3. DNA sequencing

Molecular diagnostics have been widely used in the diagnosis of hereditary diseases, prenatal gene diagnosis and the localization of disease-related genes. Gold standard for the diagnosis of CD is the identification of molecular gene defects [7,47]. DNA sequencing method is accurate and highly specific. DNA sequencing for the products of the polymerase chain reaction (PCR) was performed by terminal marking double deoxygenation and the sequencing results were compared with the normal fibrinogen gene sequences in the gene database. A definitive diagnosis can be made by demonstrating the molecular defect. Almost all patients with CD have genetic testing and the specific mutation sites

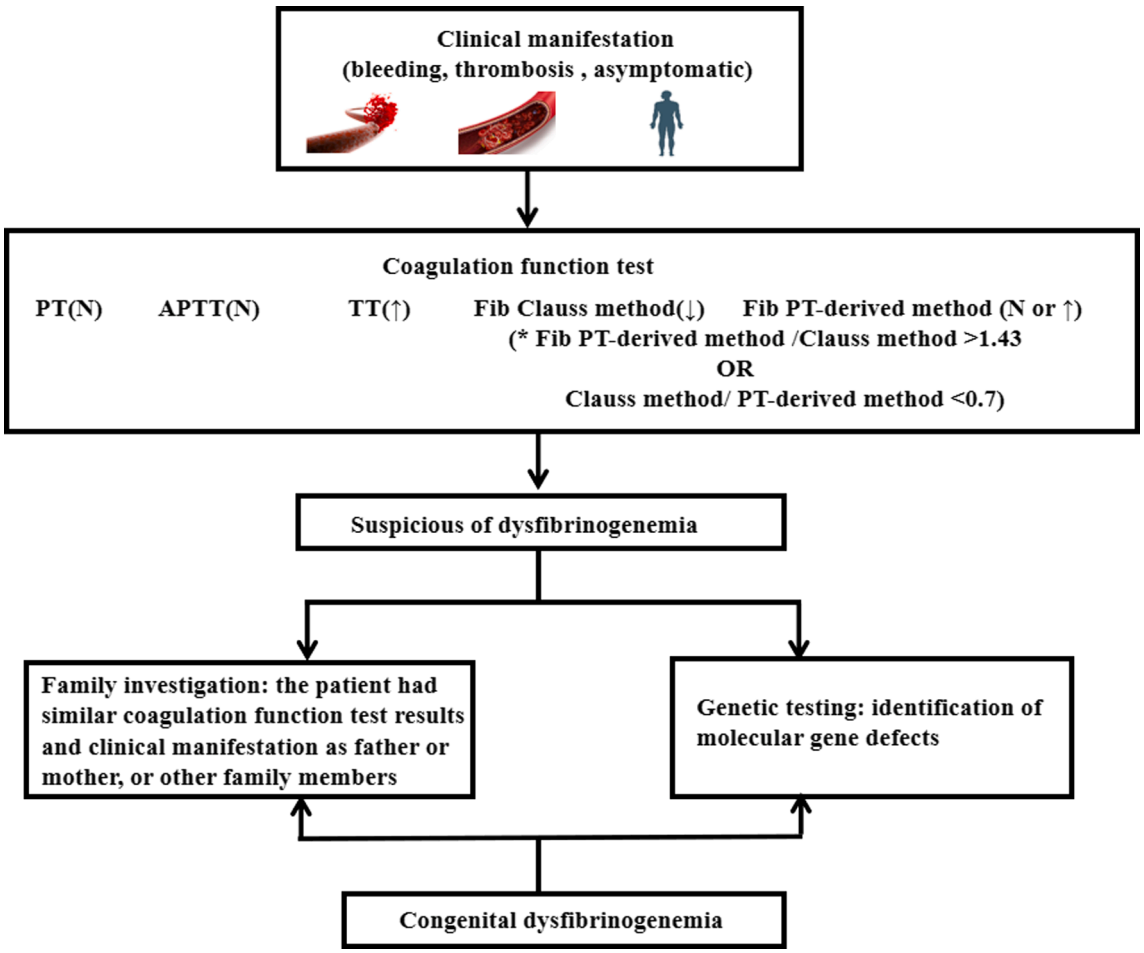

Fig. 1. Diagnostic criteria of congenital dysfibrinogenemia. PT, prothrombin time; APTT, activated partial thromboplastin time; TT, thrombin time; Fib, fibrinogen.

are almost summarized on the Human fibrinogen database website [Human fibrinogen database-Groupe d'etude sur l'hemostase et la thrombose (geht.org)]. But DNA sequencing may be time-consuming and expensive. It is not suitable for rapid clinical diagnosis. For patients with suspected CD, or to clarify the correlation between gene mutation and clinical manifestations of bleeding and thrombosis in patients, molecular biological techniques such as DNA sequencing could be used to identify the fibrinogen mutation gene locus [48], such as Bβ14Arg → Cys and Aα554Arg → Cys mutations suggesting an association with increased risk of thrombosis [49].

3.4. *Diagnostic criteria of congenital dysfibrinogenemia*

The existing CD diagnostic criteria are mentioned in the China fourth edition of the book named Diagnostic and Therapeutic Criteria for Hematologic diseases: TT and RT prolonged, PT and APTT are also prolonged in most CD patients, the plasma fibrinogen content measured by biochemical method was lower than that measured by immune method, and the fibrinogen activity/antigen ratio was <0.7. The previous about CD diagnostic had been concluded that routine parameters of coagulation (such as PT and APTT) are prolongation or coagulation tests of CD patients are infinitely prolonged [1,7,50]. An Update of mutations accounting for congenital fibrinogen disorders in 2022 showed that dysfibrinogenemia of PT and APTT were usually prolonged [51]. But Zhou et al. and other studies reported CD patients displayed normal APTT and PT [18,19,29,30]. One study included 31CD patients from northern Slovakia showed that the median of APTT was 28.75 s (normal range 22.0–32.0 s) and a median of PT was 68.5 % (range 75–125 %) and the results of PT did not increase but decreased [52]. 14CD patients from Polish showed the normal PT or APTT [53]. It can be seen that PT and APTT of CD patients are generally not prolonged in clinical case reports. Therefore, the statement in the previous diagnostic guidelines of CD that PT and APTT usually prolong is not true. And some literatures have reported the clinical manifestations of CD that approximately 50 %–55 % are asymptomatic [7,54,55]. A clinical study in Southern Italy was conducted on a group of patients with congenital abnormalities of fibrinogen including 18 patients (four afibrinogenemic patients, five hypofibrinogenemic patients, and nine dysfibrinogenemic patients) and found that 88.8 % CD patients are asymptomatic [56]. Nearly 70 % of reported 102 Chinese CD patients were found to be asymptomatic [29]. Therefore, the proportion of asymptomatic CD patients should be much greater than 50 %.

At present, the main reason for the misdiagnosis of CD patients reported in the literature is that the fibrinogen level is very low after only using of Clauss method to detect fibrinogen [20,21,57,58]. The patient was easy diagnosed with hypofibrinogenemia or other abnormal diseases [59]. If only PT-derived method is used to detect fibrinogen concentration, the results are normal or increased. The patients may be missed diagnosis. So, it is better that PT derived method combining with Clauss method can be effective for the congenital fibrinogen disorders diagnosis. Many studies have shown that using the combination of Clauss method and PT derived method to detect fibrinogen can better help correct diagnosis of CD, which can avoid misdiagnosis [21,32,42,58,60,61].

According to the existing experimental diagnosis technology, literature and combining with our research results, the simple, practical and effective diagnostic criteria of CD was proposed [62] (Fig. 1): (1) clinical manifestations: most patients were asymptomatic and a small number of

patients had the manifestation of thrombosis or bleeding; (2) coagulation function test: the results of PT and APTT are normal and TT is prolonged. Fibrinogen (Clauss method) was significantly reduced and fibrinogen (the PT-derived method) is normal or increased. The fibrinogen antigen/activity ratio (PT-derived method /Clauss method) is higher than 1.43 or fibrinogen Clauss method/PT-derived method is less than 0.7; (3) family investigation: the majority of patient were autosomal dominant inheritance. The patient had similar coagulation function test results and clinical manifestation as father or mother, or other family members; (4) genetic testing: gold standard for the diagnosis of CD is the identification of molecular gene defects. For the suspicious of CD patients, in order to clarify the correlation between gene mutations and clinical manifestations of bleeding and thrombosis, defective gene testing of fibrinogen is required.

4. Management of congenital dysfibrinogenemia

As for the quality fibrinogen disorders, there is no strong evidence-based guideline for the management of CD patients [63,64]. The related clinical management of different symptoms of CD were discussed and summarized according to guidelines, literature review and recommendations.

4.1. Asymptomatic

Most patients with CD are asymptomatic. These asymptomatic patients do not require preoperative administration of cryoprecipitate or fresh frozen plasma if their personal and family histories had no abnormal bleeding or thrombotic events. Four asymptomatic CD patients were reported that they did not receive special treatment and management before the major surgery (including valve replacement, brain surgery, tumorectomy, hysterectomy) and they all had a smooth operation [32]. And another CD patient was reported that she was misdiagnosed with hypofibrinogenemia and received infusion with fresh plasma and cryoprecipitate for ten consecutive days in the local hospital, but the concentration of fibrinogen in the body was difficult to reach 1 g/L after infusing fibrinogen. In the end, this asymptomatic patient was correctly diagnosed with CD and underwent artificial abortion without any transfusion treatment [20]. The possible reason is that the dysfunctional fibrinogen can interfere with the function of the infused fibrinogen and its detection results [65,66]. Excessive fibrinogen in the body can't be correctly detected, which is easy to increase the risk of thrombosis events in patients. Zhou et al. reported a CD patient who was misdiagnosed as hypofibrinogenemia. Then this patient was received fibrinogen infusion and then developed pulmonary embolism [67]. 74-year-old asymptomatic CD patient without personal or family history of bleeding or thrombotic event experienced bilateral severe knee osteoarthritis occurred DVT involving the intramuscular calf vein and the peroneal vein of the operated leg after fibrinogen replacement therapy during the first perioperative period [68].

Transfusion may not only induce anaphylactic reaction, but also have an increased risk of thrombotic event or blood borne infection, like hepatitis C virus or human immunodeficiency virus and so on [66]. All these will increase both the financial burden of patients and health risk. Therefore, the treatment of asymptomatic CD patients should be combined with personal and family history of bleeding or thrombosis.

4.2. Bleeding

Bleeding in patients with CD can show different forms, including the cutaneous bleeding, menorrhagia, oral bleeding, epistaxis and so on [69]. CD patients with bleeding are usually mild and not fatal. A multicenter study that included 101CD patients showed that the most common bleeding symptoms were menorrhagia (29.4 %), cutaneous bleeding (20.8 %), bleeding after surgery (8.9 %), and gastrointestinal bleeding (3.6 %) [70]. A study from Iranian reported that menorrhagia and easy bruising were the common symptom of 10CD patients with bleeding [71]. Another study from northern Slovakia also showed that the menorrhagia was the main bleeding symptom in the 31CD patients [52]. Of course, there are also some specific bleeding symptoms. A 5 years old CD male child was along with subdural hematoma, which is a very unusual presentation in dysfibrinogenemia [72]. And a 59-year-old female who was diagnosed with CD showed recurrent gastrointestinal bleeding, which is the rare cause of bleeding [73].

For patients with potentially acute bleeding, gastrointestinal bleeding or those requiring surgery, studies have reported related treatment of these CD patients with bleeding. The treatment of congenital fibrinogen deficiency may consider that the severity and location of the bleeding, the urgency of the situation or family history [1,74]. The bleeding of treatment included transfusion therapy and non-transfusion therapy. For some patients with mild bleeding, non-transfusion therapy may be sufficient for bleeding cessation. Non-transfusion therapy mainly used the anti-fibrinolytic drugs, such as tranexamic acid or e.g. ε-aminocaproic acid. If bleeding continues, transfusion therapy should be considered. Fibrinogen replacement products include fresh frozen plasma (FFP), cryoprecipitate and plasma-derived fibrinogen concentrate. Fibrinogen concentrate is generally considered the best choice for the treatments of fibrinogen deficiency. Firstly, plasma-derived fibrinogen concentrates are safer than cryoprecipitates and FFP in view of safety steps for virus inactivation [75]. Furthermore, more precise dosing can be accomplished with fibrinogen concentrates because their potency is known, in contrast with FFP or cryoprecipitates [76]. So, it is advised that cryoprecipitate and FFP should be administered only in emergency situations where fibrinogen concentrate is not available [77]. The recommended dosage of fibrinogen concentrate is listed below [64]:

(1) CD patients with bleeding manifestations require minor surgery or the bleeding is mild, consider tranexamic acid 15–20 mg/kg or 1 g four times daily alone.
(2) CD patients with bleeding manifestations require major surgery or the bleeding is severe. The recommended dosage of fibrinogen concentrate is 50–100 mg /kg, repeated in small doses at 2-4d intervals as necessary to maintain fibrinogen activity >1.0 g/l.
(3) CD patients who have a personal or family history of severe bleeding or fibrinogen activity <0.1 g/l, long-term prevention may be considered, initially using fibrinogen concentrate 50–100 mg/kg once a week in order to maintain fibrinogen activity >0.5 g/l.
(4) In the absence of fibrinogen concentrate, cryoprecipitate was advised with 15–20 ml/kg.

Or using the following formula calculate the amount of fibrinogen required as follow [78]:

$$\mathrm{Dose(g)} = 0.07 * \text{desired increment} * \{\frac{g}{l}\}(1 - \mathrm{Hematocrit}) * \text{patient weight (kg)}$$

In different clinical situations, the target of fibrinogen replacement therapy is that the concentration of fibrinogen reaches more than 100 mg/dl until healing complete, more than 50 mg/dl in minor surgery and more than 50 mg/dl with spontaneous bleeding. In addition, the side effects of fibrinogen replacement therapy should be pay special attention. As mentioned above, transfusion therapy causes inhibitory antibodies, allergic reactions and common thrombosis events[79]. Although the type, dose, and frequency of fibrinogen replacement therapy have been accurately assessed, 30 % of patients still have a risk of venous or arterial thrombosis [80]. There are currently two different concentrated forms of fibrinogen (RiaSTAP and Fibryga) approved in the United States for the treatment of afibrinogenemia and hypofibrinogenemia and not for the treatment of dysfibrinogenemia [81]. The lack of approval for dysfibrinogenemia is that thrombotic events are more likely to occur in patients with CD after fibrinogen replacement therapy [81]. Thrombin

Table 1
High risk thrombus phenotypes of dysfibrinogenemia.

Mutation site	Name	Manifestation	Authors
Aα(554) Arg>Cys	CHAPEL HILL III	Thrombus	[1] Wada Y et al. 1994
	DUSART / PARIS V (4 cases)	Thrombus	[2] Koopman J et al. 1993
	HANNOVER II	Thrombus	*Meyer M et al. 1999
	HANNOVER XI	Thrombus	*Czwalinna A et al. 2001
	NASHVILLE (11 cases)	Thrombus	[3] Tarumi T et al. 2000
	SCANDINAVIA (5 cases)	Thrombus	[4] Ramanathan R et al. 2013
	DALLAS	Bleeding and thrombus	[5] Shen YM et al. 2014
	MULTINATIONAL	Asymptomatic	[6] Casini A et al. 2015
	SOUTH ITALY D4 (2 cases)	Thrombus	[7] Santacroce R et al. 2006
Aα(532) Ser>Cys	Caracas V	Thrombus	[8] Marchi R et al. 2000
Bβ(14) Arg>Cys	CHRISTCHURCH II	Thrombus	[9] Brennan SO et al. 1997
	CHRISTCHURCH III	Thrombus	[9] Brennan SO et al. 1997
	IJMUIDEN	Thrombus	[10] Koopman J et al. 1992
	Nijmegen	Thrombus	[11] Koopman J et al. 1992
	LONDON VIII	Thrombus	[12] Vakalopoulou S et al. 1999
	SEATTLE	Asymptomatic	*Pirkle H et al. 1987
	VICENZA III	Thrombus	[13] Castaman G et al. 2005
	SAINT-GERMAIN III	Thrombus	[14] de Raucourt E et al. 2006
	UNITED KINGDOM	Thrombus	[15] Shapiro SE et al. 2013
	MULTINATIONAL	Thrombus	[6] Casini A et al. 2015
	Italian (3 cases)	Thrombus	[16] Castaman G et al. 2019
Bβ(68) Ala>Thr	Naples	Thrombus	[17] Koopman J et al. 1992
	CHINESE (5 cases)	Thrombus	[18] Zhou J et al. 2015
	HAMAMATSU	Thrombus	*Yoshida S et al. 2017
γ(364) Asp>Val	MELUN	Thrombus	[19] Bentolila S et al. 1995

The references of Table 1 was listed in supplementary table.

generation in afibrinogenemic was higher than in normal plasma and the adsorption of thrombin to fibrin was defined as "Antithrombin I" activity [82]. During the fibrinogen replacement therapy for afibrinogenemia, the increased thrombin generation was mitigated by therapy [82]. And evidence suggested that an adequate fibrinogen replacement may decrease the prothrombotic risk during the treatment of afibrinogenemia [83]. So, during replacement therapy for CD patients, more attention should be paid to the occurrence of thrombus complications. Especially for some high-risk groups (such as thrombophilia patients), low-molecular-weight heparin (LMWH) may be considered to use when patients receiving fibrinogen replacement therapy [1].

4.3. Thrombosis

There are not many CD patients with thrombotic manifestations. The prevalence of dysfibrinogenemia with thrombosis is rather low and an occurrence rate of less than 0.5–1 % had been reported in several studies comparing with other coagulation abnormalities [84]. 9 studies from 7 countries on 2376 patients had concluded that the prevalence of dysfibrinogenemia in patients with a history of venous thrombosis was low to 0.8 % [85]. And a study from northern Slovakia that included 31CD patients showed that no patients experience thrombosis events [52]. But a study from China involves 102 Chinese patients with CD showed that 3.9 % CD patients had thrombosis [29].

The exact mechanism by which dysfibrinogenemia increases the risk for thrombosis is unknown [55]. Two mechanisms may be related with thrombosis in CD patients:(1) the abnormal fibrinogen is defective in binding thrombin, which results in elevated levels of thrombin, (2) fibrin clot resistant to plasmin degradation, which results in defective fibrinolysis [76]. Clinical studies have shown that increased fibrin fiber density and resistance to fibrinolysis highly associate with risk for thrombosis [86]. There are also several fibrinogen mutation sites leading to defects in polymerization or defective assembly of the fibrinolytic system that have been identified as associated with thrombus formation [79].

According to the report, these thrombophilic mutation sites were mainly found in the C-terminal domain of the Aa chain and the thrombin cleavage site of the Bb chain [28]. Such as, fibrinogen Paris V (Aα Arg554Cys) has thrombogen-promoting properties, including poor plasminogen binding, impaired plasminogen activator activation in fibrino-dependent tissues, and an increased tendency to self-bind [87] and fibrinogen Dusart (Aα Arg554Cys) was shown to have defective plasminogen activation as well as increased clot rigidity [88]. The fibrinogen Aα Arg16Cys mutation results in fibrinolytic resistance, which maybe related with thrombosis [89] and Luo et al. reported thrombogenic fibrinogen Aα Arg16Cys may be attributed to fibrinolytic resistance due to abnormal clot structure of the fibrinogen and fibrinogen albumin complexes [18]. And the aforementioned Bβ14Arg → Cys mutations suggesting an association with increased risk of thrombosis [49]. So, the thrombotic-related dysfibrinogenemia should be considered in carriers of known mutations increasing the thrombotic risk [46,50]. Table 1 listed some of high risk thrombus phenotypes of dysfibrinogenemia [46].

Thrombophilia is a group of diseases that are prone to thrombosis due to genetic or acquired factors. Typical thrombophilia includes factor V Leiden mutation, antithrombin III deficiency, protein C or S deficiency, or prothrombine-related thrombosis [90]. Now, some types of CD are also included in genes related with thrombophilia [91,92]. It is worth considering whether asymptomatic CD patients should be prophylactic anticoagulation in advance if carriers of thrombotic-related fibrinogen mutation (such as BβArg14Cys and AαArg554Cys). These studies seem to suggest that patients with fibrinogen mutations associated with an increased susceptibility to thrombosis should be treated with anticoagulation [63,87,93]. The suggestions of management of CD patients with thrombosis based on related-guidelines and literature reviews [50,63,64,92,94,95].

(1) If the CD patient has the thrombotic event, LMWH is generally used for anticoagulation therapy. After the end of thrombosis treatment, the risk of thrombosis recurrence and the possibility of bleeding should be fully evaluated and the duration of treatment was determined based on the personal and family history, as well as the presence of other potential thrombophilic conditions.
(2) If there is a personal or family history of thrombotic events, it should be accurate thromboprophylaxis when exposed to risk factor (such as major surgery).
(3) If CD patients with high risk thrombus phenotypes, prophylactic anticoagulation is usually required in high-risk situations (such as major surgery).

4.4. Pregnancy

Fibrinogen play a critical role in the pregnancy, as fibrinogen is essential for sustaining the development of foetal-maternal circulation,

for supporting the early term trophoblast proliferation and spreading and for the development and maintenance of the placenta, for stabilizing embryo implantation. During the delivery, fibrinogen is also a major determinant for preventing excessive bleeding resulting from the placental separation [96,97]. Studies had reported that women with dysfibrinogenemia may have greater risk of pregnancy complications than the general population, including spontaneous abortion, placental abruption, post-partum thrombosis or hemorrhage and so on [85,98].

About management of CD patients during pregnancy, it was suggested that the management can be by a multidisciplinary team (MDT) and preconception counseling should be carried out with adequate information on the clinical and genetic implications of the CD [94]. During the antenatal care, fibrinogen should be monitored at least monthly and ultrasound for monitoring fetal and placenta development is necessary [74]. The patient's personal and family history of bleeding or thrombosis are important guides for management [78].

According to the different clinical situation, it is recommended to adjust the dosage of fibrinogen supplementation as follows [64]. However, simultaneous consideration should be given to the necessity of anticoagulant therapy during fibrinogen supplementation.

(1) Pregnancy CD patients with a personal or family history of bleeding or with previous adverse pregnancy outcomes, consider prophylaxis throughout pregnancy with fibrinogen concentrate initially 50–100 mg/kg twice per week, adjusted to maintain trough fibrinogen activity >1 g/l. Consider additional fibrinogen concentrate at established labour to ensure fibrinogen activity >1.5 g/l for at least 3 days.

However, current international guideline recommendations are mainly based on observational and retrospective data and the indications, intensity and duration of thromboprophylaxis in certain at-risk populations during pregnancy and puerperum are still uncertain [99]. There is also lack of large-scale studies on the treatment of CD patients with thrombosis during pregnancy. The management for pregnancy CD patients with thrombotic based on guidelines and recommendations [50,64,100–102].

(2) If pregnancy CD patients with the personal history of thrombosis, thromboprophylaxis with LMWH should be considered throughout the pregnancy and the postpartum period.
(3) Pregnancy CD patients with family history of thrombotic, the related guidelines recommend postpartum thromboprophylaxis for at least 6 weeks with LMWH.

Some type of thrombophilia (such as heterozygous factor V-Leiden, prothrombin G20210A mutation, protein C or S deficiency) were defined as lower risk thrombophilia. Dysfibrinogenemia had been divided into two categories (3A and 3B). 3B is mainly thrombotic-related dysfibrinogenemia (carriers of an established thrombotic fibrinogen mutation) or suffering from thrombotic events [46]. Thrombotic fibrinogen mutation can be further classified as low risk of thrombus phenotypes or high risk of thrombus phenotypes. Most carriers of mutations listed in Table 1 have thrombotic manifestations and them can be classified as high risk of thrombus phenotype. However, the 'low thrombotic risk phenotype' is not well defined. CD patients with the same mutation may have different clinical phenotypes. Such as AαArg16Cys, some patients with this mutation site are asymptomatic or thrombotic and asymptomatic are much than thrombotic phenotype [103,104]. In the future, a method is needed that can better and accurately classify the thrombus risk phenotype accurately, which make accurate therapeutic interventions for patients. Asymptomatic CD women (without personal and family history of bleeding or thrombotic events) should be observed closely but no specific treatment is required unless bleeding or the family history suggests bleeding is likely [78]. Chen et al. reported an asymptomatic 23-years-old pregnancy CD woman with fibrinogen activity 0.41 g/l didn't receive transfusion treatments and the delivery process went well. There was no massive bleeding or thrombosis after delivery [57]. Yan et al. also reported a 30-year-old CD patient without any treatment had a successful pregnancy and childbirth [21]. In the clinical work, the treatment of asymptomatic CD patients should remember not to blindly over-transfusion therapy.

Table 2
Management of congenital dysfibrinogenemia.

Congenital Dysfibrinogenemia	Management
1. Asymptomatic	
CD patients without bleeding or thrombosis	The CD patient's personal and family history are important guides for management. Asymptomatic patients do not require treatment other than close observation.
2. Bleeding	
I. CD patients require minor surgery or the bleeding is mild	Tranexamic acid 15-20mg/kg or 1g four times daily alone;
II. CD patients require major surgery or the bleeding is severe	The recommended dosage of fibrinogen concentrate is 50-100mg /kg, maintaining fibrinogen activity >1.0 g/l;
III. CD patients with personal or family history of severe bleeding or fibrinogen activity <0.1 g/l	Long-term prevention may be considered, with 50-100mg/kg once a week maintaining fibrinogen activity >0.5 g/l;
3. Thrombosis	
I. CD patient with the thrombotic event	LMWH is generally used for anticoagulation therapy;
II. CD patient with the personal or family history of thrombotic events	Accurate thromboprophylaxis is required when exposed to risk factor (such as major surgery);
III. CD patients with high risk thrombus phenotypes	Prophylactic anticoagulation is usually required in high-risk situations (such as major surgery).
4. Pregnancy	
I. Pregnancy CD patients with personal or family history of bleeding or with previous adverse pregnancy outcomes	Consider prophylaxis throughout pregnancy with fibrinogen concentrate initially 50–100 mg/kg twice per week, maintaining fibrinogen activity>1g/l. Fibrinogen activity maintain >1.5 g/l for at least 3 day at the labour;
II. Pregnancy CD patients with the personal history of thrombosis	Thromboprophylaxis with LMWH should be considered throughout the pregnancy and the postpartum period;
III. Pregnancy CD patients with family history of thrombotic	Postpartum thromboprophylaxis for at least 6 weeks with LMWH;
IV. Pregnancy CD patients with high risk thrombus phenotypes	Both antepartum thromboprophylaxis and postpartum are recommended;
V. Pregnancy CD patients without personal and family history of bleeding or thrombotic events	Patients do not require any treatment other than close observation.

Now guideline recommendations had different opinion on the topic of thromboprophylaxis in asymptomatic thrombophilia. Relevant guidelines or studies indicate that the treatment of asymptomatic thrombophilia based on the level of risk of thrombophilia or the family history of thrombotic. The CD patient's personal and family history of bleeding or thrombosis are important guides for management. Combination with related guideline recommendations, it is summarized as follow [64,100–102].

(4) Pregnancy CD patients with high risk thrombus phenotypes, both antepartum thromboprophylaxis and postpartum are recommended during the pregnancy.
(5) Pregnancy CD patients without personal and family history of bleeding or thrombotic events should be observed closely but no specific treatment.

5. Conclusion

CD is not the rare disease. However, as a matter of fact, many clinical workers are not familiar with this disease, so patients are easy misdiagnosed and mistreated. Misdiagnosis and unnecessary transfusion treatments bring huge health risks to patients. An accurate diagnosis of congenital fibrinogen disorders is the fundamental to optimize the patient's management [41]. According to the existing experimental diagnosis technology, literature and combining with our research results, the simple, practical and effective diagnostic criteria for CD were concluded. Based on the relevant literature and existing treatment guidelines, more comprehensive treatment recommendations are summarized (Table 2). The treatment of CD patients should consider the patient's personal and family history of bleeding or thrombosis. In addition, during course of clinical treatment, management is chosen on patient's clinical profile balancing bleeding risk and thrombosis progression. So, optimal plasma fibrinogen threshold for sufficient hemostasis and minimal thrombosis is still needed to determine by more prospective studies for now [79].

CRediT authorship contribution statement

Jie Yan: Resources, Writing – original draft, Writing – review & editing. **Lin Liao:** Methodology, Writing – review & editing. **Donghong Deng:** Methodology, Writing – review & editing. **Weijie Zhou:** Validation, Writing – review & editing. **Peng Cheng:** Resources, Writing – review & editing. **Liqun Xiang:** Writing – review & editing. **Meiling Luo:** Methodology, Writing – review & editing. **Faquan Lin:** Project administration, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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Appendix A. Supplementary data

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