Diagnosis and Management of Dysfibrinogenemia

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**H&O** What is dysfibrinogenemia, and how common is it?

**SS** Dysfibrinogenemia is a qualitative functional disorder of fibrinogen. It is characterized in the laboratory by reduced fibrinogen activity compared with the fibrinogen antigen level. A ratio of functional activity to antigen level of less than 0.7 is suggestive of dysfibrinogenemia, although the sensitivity and specificity of this cutoff have not been prospectively validated. Dysfibrinogenemia may be heritable or acquired. Heritable dysfibrinogenemia (HD) is rare, with a prevalence of approximately 15 per 100,000 people. Acquired dysfibrinogenemia—which is usually caused by liver disease—is more common but is not in itself associated with increased bleeding risk, so no hemostatic intervention is required.

**H&O** How does the condition typically present?

**SS** In database and registry reports of HD, most patients were asymptomatic at presentation, 25% had bleeding (usually mild and typically mucocutaneous, traumatic, or surgical), and 20% had venous or arterial thrombosis. More rarely, HD has been associated with poor wound healing and pregnancy complications.

In a study we published in 2013 in the *British Journal of Haematology*, we reviewed 35 patients with a diagnosis of HD across 2 centers in the United Kingdom: 23 index cases and 12 affected first-degree relatives. HD was identified in specialist hemostasis clinics in 52% of the index cases (10 during investigation for a bleeding disorder and 2 following venous thrombosis). In the remaining 48% of the index cases, HD was identified during further investigation of abnormal clotting screen results, most of which were routine investigations before elective surgery.

**H&O** How is HD diagnosed?

**SS** The initial workup should include fibrinogen assays (activity and concentration) and measurement of the prothrombin time (PT), activated partial thromboplastin time (APTT), thrombin time (TT), and reptilase time (RT). Genetic analysis should be used to confirm the diagnosis.
Fibrinogen activity is measured routinely in clinical laboratories. It is either measured by the Clauss fibrinogen assay (a true functional assay) or derived from the change in light scatter or transmission during measurement of the PT time (PT-derived fibrinogen). The latter test is not recommended for hemostatic investigations, and results show marked discordance with those of the Clauss fibrinogen assay in patients who have HD, overestimating fibrinogen by a factor of 5 or 6. Most people with HD have reduced fibrinogen function when the Clauss fibrinogen assay is used, although an exercise in 2017 across 86 laboratories participating in the United Kingdom National External Quality Assessment Scheme (UK NEQAS) for Blood Coagulation and the Prospective Rare Bleeding Disorders Database (PRO-RBDD) study highlighted the potential for rare variants to be missed on the Clauss fibrinogen assay. Testing of fibrinogen Longmont, a rare variant associated with a bleeding tendency, with the Clauss fibrinogen assay yielded markedly different results when various reagents were used. Fibrinogen Bordeaux (FGC p.Arg439Cys) has a similar coagulation pattern but is associated with a thrombotic phenotype.

Several assays are available to measure the physical amount of fibrinogen, as opposed to its activity. The reference method is total clottable fibrinogen, which is measured by weight (dry clot weight), although immunoassays such as enzyme-linked immunosorbent assay (ELISA) can also be used in the diagnosis of dysfibrinogenemias.

In most cases, HD results in prolonged thrombin and reptilase clotting times. However, the effects of HD on PT and APTT are inconsistent and depend on the choice of laboratory method. In our study published in 2013, we used a variety of laboratory techniques to measure the PT and APTT of patients with HD, and only the PTs determined with the Sysmex CA-1500 System and Innovin activator were consistently abnormal. Turbidimetry curves generated by the Sysmex CA-1500 System (Siemens Healthineers) during clot formation in the PT test showed delayed onset and slower increase in turbidity when samples from patients with HD were compared with samples from controls, although the absolute changes in turbidity were similar. This finding is consistent with delayed polymerization in HD plasma. Because the Sysmex CA-1500 System defines the PT endpoint as the time taken to reach 50% of the maximum change in side scatter after clotting initiation, both the delayed initiation and reduced rate of clot formation in HD plasma are expected to contribute to delay in reaching this endpoint and therefore prolong the PT. This effect is not observed during the APTT test because thrombin generation is slower, which may mask the slower polymerization of dysfibrinogens with polymerization defects. Similarly, other coagulometers use PT endpoints determined according to plasma viscosity (STA-R Evolution, Diamond Diagnostics) or other turbidity curve parameters (IL ACL Futura, Block Scientific; MDA II, Biomerieux) that are less affected by a delay in fibrin polymerization.

**H&O** Can one predict if a dysfibrinogenemia is more likely to be prothrombotic or prohemorrhagic?

**SS** This is an interesting and really important question, and one that illustrates how genetic analysis and databases can provide crucial information. No consistent relationship has been found between the results of basic laboratory tests (TT, RT, Clauss fibrinogen assay, dry clot weight) and either bleeding or thrombosis. Some interesting work has been done in this area with viscoelastic hemostasis assays, such as thromboelastography (TEG) and thromboelastometry (ROTEM). Zhou and colleagues in 2015 reported that TEG parameters did not differ between patients who had HD with and HD without bleeding; however, the same group did find an increased risk for adverse outcomes of obstetric complications in women with abnormal TEG parameters, in particular a decreased maximal absorbance in the TEG functional fibrinogen assay (odds ratio, 20; 95% CI, 1.97-203.32). In 2016, Casini and colleagues published a retrospective study of 24 patients with HD suggesting that increased permeability and prolonged clot lysis times were associated with bleeding and thrombotic phenotypes, respectively; however, most clinical laboratories do not have access to these techniques.

The family history is important, especially for patients with mild phenotypes, because it will reveal the effects of other genetic and environmental modifiers of phenotype, such as factor V Leiden and the prothrombin G20210A mutation. The most valuable predictors regarding phenotype are genetic analysis and related information in databases. It is important to review the information because some of the phenotypic associations described with specific mutations are weak; however, a few genetic defects have been described that are strongly associated with a thrombotic phenotype and are therefore predictive, such as the Caracas V, Vlissingen, and Melun fibrinogens.

**H&O** How is HD treated, and how strong are the data to support standard treatment?

**SS** HD is rare and heterogenic, so guidelines are limited and generally based on expert consensus opinion, such as the United Kingdom Haemophilia Centre Doctors’ Organization (UKHcido) guidelines for rare coagulation disorders. Patients should be under the care of a specialist hemostasis center. They should be managed...
individually on the basis of their personal history of bleeding and thrombosis, family history, genetic analysis, and comorbidities.

We advise those with a bleeding tendency to avoid medicines that interfere with platelet function. We also provide local control of bleeding, such as use of a combined oral contraceptive pill for menorrhagia and cauteryization for nosebleeds. Tranexamic acid can be used for minor bruising or as a preventative before procedures. For most patients, such management will probably suffice. However, for patients with a significant bleeding phenotype, the administration of fibrinogen concentrate should be considered before a significant invasive procedure or if the patient is actively bleeding. In studies of patients with hypofibrinogenemia, fibrinogen concentrate at 50 to 100 mg/kg every 2 to 4 days, to achieve a fibrinogen activity level above 1.0 to 1.5 g/L, was usually sufficient to treat or prevent spontaneous or surgical bleeding.

Individuals experiencing thrombosis or with a strong predictive genetic mutation for thrombosis should also be treated in a specialized hemostasis center. For patients with a thrombotic tendency, we advise avoidance of systemic estrogen and the use of extended thromboprophylaxis at times of high risk, such as surgery. Venous thrombosis in patients with HD has been managed with low-molecular-weight heparin (LMWH), with warfarin anticoagulation for the long-term prevention of recurrent thrombosis. In the latter case, PT/INR reagents must be used that are not affected by the dysfibrinogen at baseline. The direct oral anticoagulants now offer an alternative option for the prevention of both acute and secondary venous thrombosis.

**H&O** How do you decide whether to use purified fibrinogen concentrates or cryoprecipitate for fibrinogen replacement therapy?

**SS** In the United Kingdom, we use purified plasma-derived fibrinogen concentrate rather than cryoprecipitate for patients with HD. The preparation of the concentrate incorporates additional steps for the inactivation/removal of viruses, so that the risk for transmission is extremely low, and the concentrate is relatively easy to give. The variation in fibrinogen content is greater in cryoprecipitate than in fibrinogen concentrate, and cryoprecipitate may be associated with transfusion reactions or volume overload.

**H&O** How do you avoid thrombotic complications with fibrinogen replacement therapy?

**SS** Case series of replacement with fibrinogen concentrate have described rates of venous or arterial thrombosis as high as 30% following replacement, although these events occurred mainly in patients with a fibrinogenemia. In dysfibrinogenemia, very few data are available to guide fibrinogen replacement. Our approach is to be relatively cautious and use fibrinogen concentrate judiciously. Unless someone has a definite bleeding phenotype, we suggest avoiding the administration of fibrinogen before an invasive procedure but keeping it on standby. If the patient is bleeding, then we initially aim to treat at the doses discussed previously to a target fibrinogen activity level above 1.0 g/L. However, we recently had a patient who, when given fibrinogen concentrate at 50 mg/kg, exhibited a very small increase in the fibrinogen level as measured with the Clauss fibrinogen assay but showed a good response on ROTEM with an acceptable FIBTEM value. We therefore used FIBTEM to guide fibrinogen replacement therapy to adequate hemostasis.

**H&O** Should one prescribe venous thrombosis prophylaxis with LMWH to patients receiving fibrinogen replacement therapy?

**SS** No studies are available to guide this decision. We would consider LMWH prophylaxis on an individual basis, depending on the reason for giving the fibrinogen replacement therapy (active bleeding or perioperative setting) and on the levels of replacement achieved.

**H&O** How should dysfibrinogenemia be managed in pregnancy?

**SS** Dysfibrinogenemia in pregnancy should be managed by a center specializing in hemostasis, with multidisciplinary discussions among specialists in hematology, obstetrics, and anesthesia. The pregnancy complications of hypofibrinogenemia include pregnancy loss, hemorrhage, placental abruption, and thrombosis. For patients with hypofibrinogenemia, it is recommended that prophylaxis be considered during pregnancy to maintain Clauss fibrinogen assay levels above 0.6 to 1.0 g/L overall and above 1.5 g/L at delivery to reduce the risk for these complications. Similar pregnancy complications have been reported in patients with HD, although case reports are very limited. HD should therefore be managed on an individual basis, with consideration of the personal and family history and mutation analysis. Successful pregnancies have been reported in patients with HD, both without any replacement therapy and with fibrinogen replacement given 2 to 3 times a week throughout pregnancy. The Clauss fibrinogen assay combined with viscoelastic assays can be used to guide replacement therapy. Prophylactic LMWH should be considered in the postpartum period, and earlier if the patient has a thrombotic phenotype.
**H&O** Should the family members of someone with HD also be evaluated?

**SS** Absolutely. The inheritance of HD classically is autosomal-dominant. Family screening is arguably most important for those patients who have a genetic mutation with strong thrombotic/bleeding associations. However, screening is also important for family members who are relatively asymptomatic because of concerns that may arise before surgery or in an emergency situation, and screening makes it possible to monitor invasive procedures carefully.

**H&O** Is hypodysfibrinogenemia less critical than dysfibrinogenemia?

**SS** Hypodysfibrinogenemia is defined as low levels of dysfunctional fibrinogen, with fibrinogen levels below the reference range of the assay used. It occurs either because of compound heterozygosity for 2 different mutations, one resulting in fibrinogen deficiency and the other in abnormal function, or because of heterozygosity for a single mutation that results in the synthesis of an abnormal fibrinogen that is poorly secreted. Hypodysfibrinogenemia is no less critical than dysfibrinogenemia because both major bleeding and recurrent thrombosis can develop in these patients. Patients with hypodysfibrinogenemia often have a relatively pronounced bleeding phenotype that is proportional to the level of circulating fibrinogen.

**H&O** Could you briefly discuss acquired dysfibrinogenemias?

**SS** The acquired dysfibrinogenemias are a heterogeneous group of disorders in which the functional activity of fibrinogen is reduced. Laboratory results show a prolonged TT and RT. Acquired dysfibrinogenemia is most commonly caused by liver diseases, including cirrhosis and acute liver failure, and a prevalence of 80% has been reported in these patients. The formation of dysfibrinogen results from the increased sialylation of carbohydrate side chains in the fibrinogen molecule, which increases the net negative charge of fibrinogen, and secretion of fibrinogen with an excess of sialic acid. Acquired dysfibrinogenemia is usually present at the time of diagnosis and disappears when the tumor is in remission, often reappearing if the tumor recurs. As mentioned earlier, acquired dysfibrinogenemias are not associated with increased bleeding and do not require intervention and treatment.

**H&O** What advances have been made over the past 5 years in our understanding of dysfibrinogenemias?

**SS** I think the major recent advances are in genetic analysis and the development of databases. Because no correlation has been found between basic laboratory assays and clinical phenotype, genetic analysis is crucial for better prediction of the phenotype. The databases have also revealed that many of the dysfibrinogenemias do not cause symptoms and do not require any intervention. It is extremely important that this research continue and that more information accumulate so that genotype-phenotype relationships can be defined.

**H&O** What should the next steps in research be?

**SS** Prospective trials exploring the use of global assays for managing these patients would be really useful. Individual centers should be encouraged to contribute to national databases and international prospective trials, such as the American Thrombosis & Hemostasis Network (ATHN) Dataset (athn.org) and the PRO-RBDD project (eu.rbdd.org, rarecoagulationdisorders.org), which will help clinicians and patients in the future.

**Disclosure**

Dr Shapiro has no disclosures to report.

**Suggested Reading**


