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Hematological Assessment of a Patient with an Inherited Bleeding Disorder

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1.1 Introduction

The inherited bleeding disorders (IBDs) are a heterogeneous group of disorders affecting the hemostatic system. In individuals in whom the underlying abnormality has been identified, the majority of IBDs are due to von Willebrand disease (VWD) and disorders of coagulation factors; a small proportion are due to abnormalities in platelet count or function or defects in the fibrinolytic system [1]. Around 2% of patients registered with a bleeding disorder do not have a classifiable disorder [1].

Individuals with IBDs may give a life-long history of excessive bruising or bleeding, but many only manifest when faced with a hemostatic challenge or are picked up incidentally by abnormal coagulation tests. Indeed some, such as certain cases of factor XI (FXI) deficiency, may not have a bleeding phenotype at all, even when exposed to hemostatic challenges. IBDs can affect all genders, but women with IBDs face added challenges related to menstruation, pregnancy, and childbirth. Undiagnosed bleeding disorders can often be the cause of heavy menstrual bleeding and also the cause of or a contributory factor for other gynecological problems, such as bleeding from the corpus luteum [2].

Women with IBDs may present with a positive bleeding history or have a known family history. Manifestations of bleeding can vary, even within the same type of disorder, because of the influence of concomitant inherited and acquired factors. An integrated clinical and laboratory assessment is therefore essential in the diagnostic work-up.

This chapter will cover the mechanisms of normal hemostasis and an approach to the clinical and laboratory hematological assessment of a patient with a suspected IBD.

1.2 Normal Hemostasis

After damage to the lining of the blood vessel wall, the body responds with physiological mechanisms to stop bleeding and maintain hemostasis, without causing more widespread thrombosis. This co-ordinated process involves components of the blood, including platelets and clotting factors, with the overall aim of forming a stable blood clot (Figure 1.1). Hemostasis is achieved through a delicate balance of pro- and anticoagulant factors to stop bleeding while simultaneously avoiding development of pathological thrombi [3].

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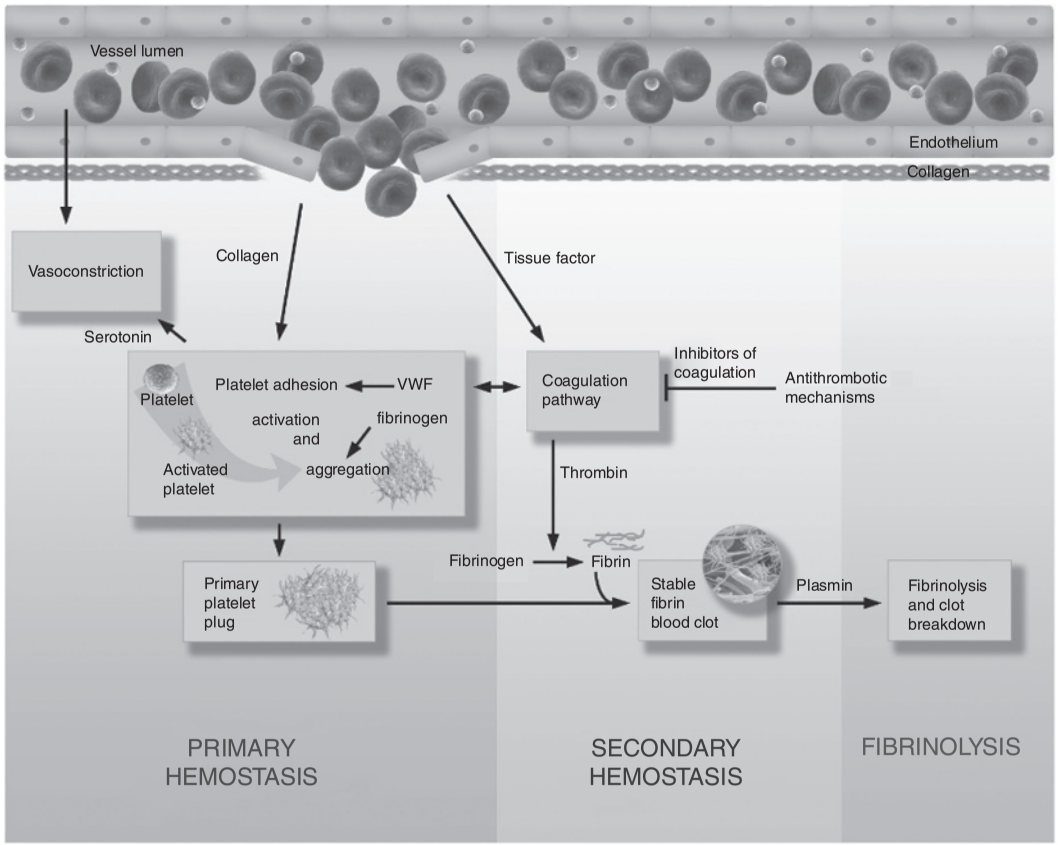

Figure 1.1 Overview of hemostasis and key components. A vascular injury exposes collagen that allows platelets to adhere via VWF to the subendothelium. Activation of platelets occurs and platelets aggregate together via VWF and fibrinogen. Primary hemostasis results in the formation of the initial platelet plug. Tissue factor activates the coagulation pathway in parallel with platelet activation; both pathways enhance each other. Fibrinolysis prevents excessive thrombus formation, through the generation of plasmin followed by the digestion of fibrin. *Source:* Modified from www.thrombocyte.com/hemostasis-definition.

1.2.1 Primary Hemostasis

In the early stages after vessel injury, interactions between platelets, the subendothelium, and adhesive proteins lead to the formation of a platelet plug (primary hemostasis). The three main steps of primary hemostasis are as follows.

1) *Platelet adhesion*: following vessel injury, von Willebrand factor (VWF) binds to specific sites on exposed collagen. Platelets adhere to the exposed subendothelial matrix (directly or indirectly via VWF). This is mediated through binding of VWF with the platelet glycoprotein GP1b, while GPVI interacts with collagen, and platelet β1 integrin with laminin, collagen, and fibronectin. These interactions enable firm adhesion of platelets to the exposed subendothelial matrix [3].
2) *Platelet activation*: platelet adhesion to the subendothelium triggers shape change and release of platelet α and dense granule contents. This activation recruits and activates additional platelets to the injured site. (Thrombin, produced by the coagulation pathway, adds to the activation of platelets.)
3) *Platelet aggregation and platelet plug formation*: thrombin cleaves fibrinogen and the resulting fibrin monomers form a bridge between activated platelets, causing platelets to aggregate together, forming a platelet plug. The GPIIb/IIIa platelet receptor is converted into its high-affinity conformation, allowing for stable interactions between the receptor and fibrin, VWF, and fibronectin.

1.2.2 Secondary Hemostasis

Secondary hemostasis usually occurs simultaneously with primary hemostasis. After endothelial damage, tissue factor (TF) is exposed, which binds to and activates FVII. The TF-FVIIa complex then stimulates generation of small amounts of thrombin and FXIa through the extrinsic pathway. Thrombin generation is amplified through the intrinsic pathway starting with FXI and through the downstream cascade including co-factors FVIII and FV (Figure 1.2). These enzymatic reactions occur on the surface of platelets and other cell surfaces. This leads to the formation of FXa on the platelet surface which, aided by its co-factor, FVa, generates

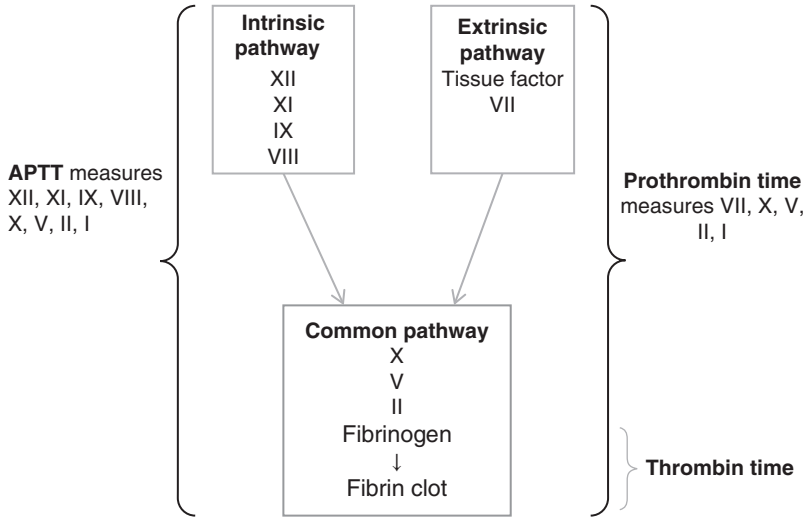

Figure 1.2 Pathways of coagulation: the intrinsic (*in vitro*) pathway as measured by the activated partial thromboplastin time (APTT) and the extrinsic (*in vivo*) pathway as measured by the prothrombin time (PT). Both intrinsic and extrinsic pathways share a common final pathway.

an explosive burst of thrombin. Thrombin catalyzes the conversion of fibrinogen to fibrin. Fibrin polymers form a fibrin network, which is stabilized by FXIII. As the clot forms, circulating red blood cells, white blood cells, and platelets become incorporated into its structure.

1.2.3 Fibrinolysis

Fibrinolysis is tightly regulated by the fibrinolytic system. Fibrinolysis is initiated by the proteases tissue plasminogen activator (tPA) or urokinase-like plasminogen activator (uPA), which convert plasminogen to the active plasmin. Plasmin cleaves fibrin and fibrinogen, leading to clot breakdown.

1.2.4 Cell-Based Model of Hemostasis

The importance of cells and cell surfaces in hemostasis is reflected in the "cell-based model of hemostasis" described by Hoffman and Monroe [4]. It is more representative of *in vivo* coagulation than the traditional "cascade model." There are three main phases in the cell-based model (Figure 1.3). The initiation phase occurs on the TF-bearing cell. Injury exposes the TF-bearing cell to flowing blood and plasma-based VIIa. The TF-VIIa complex results in the generation of a small amount of FIXa, Xa, and thrombin. In the second phase, "amplification," the small amount of thrombin activates platelets,

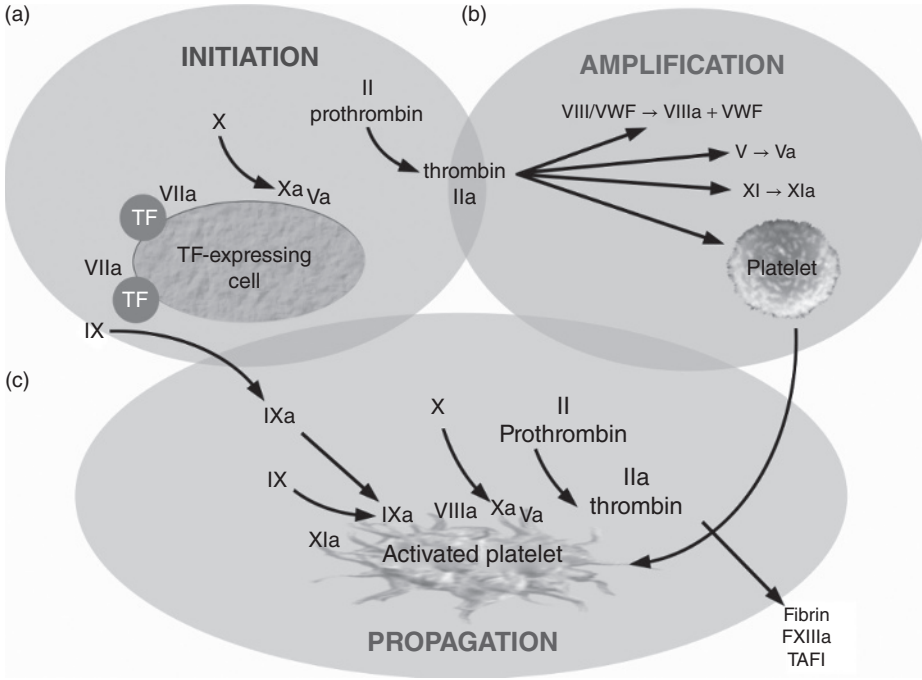

Figure 1.3 Cell-based model of hemostasis. The cell-based model comprises three overlapping stages: (a) initiation, (b) amplification, and (c) propagation. (a) *Initiation phase*: this occurs on the TF-expressing cell and is initiated when injury exposes the TF-bearing cell to the flowing blood. A small amount of FIXa, Xa, and thrombin is formed. (b) *Amplification phase*: the small amount of thrombin generated from the initiation phase activates platelets, releases VWF, and leads to generation of activated forms of FV, FVIII, and FXI. (c) *Propagation phase*: activated coagulation factors from the previous phases aggregate on the platelet surface. FVIII complexes with FIX to form the tenase complex, resulting in FXa generation on the platelet surface. The prothrombinase complex forms and results in large amounts of thrombin generation. This thrombin burst leads to fibrin formation and also activates FXIII and TAFI. FXIIIa cross-links fibrin strands to form a stable fibrin network, and TAFI protects the clot from plasmin-mediated fibrinolysis. *Source:* Adapted from Hoffman and Monroe [5] and Kessler [6].

releases VWF, and leads to generation of FVa, FVIIIa, and FXIa. The propagation phase is characterized by the migration of large numbers of platelets to the site of injury and the production of the tenase complex, which results in FXa generation on the platelet surface. The FXa generated on platelets rapidly binds to Va and converts prothrombin to thrombin. Large amounts of thrombin are generated, converting fibrinogen to fibrin. The fibrin clot is stabilized by activation of thrombin-activatable fibrinolysis inhibitor (TAFI) and FXIII.

Although the intrinsic and extrinsic pathways may be less representative of *in vivo* coagulation, an appreciation of the components of each pathway is helpful when interpreting abnormalities in the activated partial thromboplastin time (APTT) and prothrombin time (PT). Deficiencies of clotting factor may prolong the APTT (tests the intrinsic pathway) and PT (extrinsic pathway) (see Figure 1.2).

1.3 Defects of Hemostasis

The ability to achieve hemostasis and stop bleeding depends on the integrity of all components of the pathway [7] and knowledge of the underlying hemostatic defect can help with categorization of the bleeding disorder. For a patient with an undiagnosed disorder, it may be possible to predict whether the defect affects primary or secondary hemostasis from the type and pattern of bleeding elicited in the history.

The main IBDs can be categorized according to the underlying defect.

- Hemophilia – deficiency of clotting factors FVIII (hemophilia A) or FIX (hemophilia B). Patients lack amplification of the coagulation cascade by FIX with co-factor VIII [7].
- VWD, where there is deficiency of VWF and therefore impaired platelet adhesion and aggregation.
- Platelet function disorders, for example affecting the platelet receptor or platelet signaling pathways.
- Rare coagulation disorders, such as deficiency of factors V, VII, IX, and XIII or fibrinogen disorders.

1.4 Clinical Presentation of Bleeding

Inherited bleeding disorders may manifest with a variety of bleeding symptoms. There may be considerable variability in symptom severity even in patients affected by the same disorder. Acquired defects in the hemostatic system, for example caused by antiplatelet or antithrombotic medication, may exacerbate any underlying inherited disorder. Disorders of primary hemostasis often present with mucocutaneous bleeding and the early onset of bleeding after injury or trauma, compared with more delayed bleeding or overt bleeding with disorders of secondary hemostasis (abnormalities with clotting factors or fibrinolysis).

Bleeding symptoms are common in healthy individuals; over 20% of the general population report at least one bleeding symptom [8]. In addition, by chance alone, 1 in 20 people will have a result outside the "normal" reference range. Under- and overdiagnosis of bleeding disorders can have serious sequelae. Underdiagnosis will lead to inappropriate or inadequate medical treatment, but with overdiagnosis, healthy individuals can be needlessly exposed to hemostatic therapy and potential complications [9].

Menstruation, pregnancy, and childbirth present recurrent hemostatic challenges to females with and without IBDs. Menorrhagia is the most common symptom experienced by women with an IBD (up to 80% of women with IBD report menorrhagia) [10]. However, it is also common in the general population; 5–10% of women of reproductive age will seek medical attention for menorrhagia [11]. Menorrhagia may be due to endocrine, inherited bleeding or gynecological disorders but prior to comprehensive hemostatic testing, the underlying etiology was only found in ~50% of cases [12]. An IBD is found in up to

20% of women with menorrhagia and a normal pelvic examination [9, 13–15], the most common being VWD [15]. Laboratory abnormalities of hemostasis, especially platelet function defects, are common among women with unexplained menorrhagia, but their clinical significance requires further study, especially if the abnormality is mild [14].

1.5 Diagnosis

Making a diagnosis of an IBD has life-long consequences. An accurate diagnosis is important as the impact is far-reaching, especially with precautions that affect perioperative management, work, and lifestyle activities as well as implications for screening and investigation of family members. Despite the development and use of standardized bleeding assessment tools, distinguishing how to further investigate patients with bleeding symptoms can be challenging. Joint input from gynecology and hemostasis specialists is recommended to ensure the bleeding status has been thoroughly investigated in women with suspected IBD [16, 17].

1.6 Approach to a Female with a Bleeding History

1.6.1 History

A woman may present for consultation with positive bleeding symptoms related to the gynecological system or additional bleeding symptoms, or she may have a family history of a bleeding disorder. Assessment should include a history of bleeding symptoms and the site, duration, frequency, and severity of bleeding (Table 1.1). Particular enquiry should include a history of mucosal bleeding, menorrhagia, epistaxis, easy bruising, and any bleeding episodes after a hemostatic challenge such as surgery, dental extraction, childbirth (postpartum hemorrhage (PPH)), and treatment required for any bleeding episodes. Bleeding that required blood transfusion, use of hemostatic adjuncts, and antifibrinolytic agents, such as tranexamic acid, may indicate a significant or severe bleed.

Bleeding history may be subjective and specific tools have been developed to provide a more objective and standardized assessment of bleeding symptoms, for example the International Society on Thrombosis and Haemostasis (ISTH) Bleeding Assessment Tool and pictorial bleeding assessment chart for menorrhagia (see Chapter 2 for bleeding assessment tools). These standardized tools should be used wherever possible.

Although women with IBDs are more likely to experience menorrhagia, they are also at risk of other problems that may present with increased bleeding such as hemorrhagic ovarian cysts, bleeding from the corpus luteum, endometriosis, hyperplasia, polyps, fibroids, pregnancy, and childbirth [20, 21]. In women with an IBD, especially VWD, the risk of PPH is increased [22, 23] but primary PPH alone is not a good predictor of IBDs [24].

1.6.1.1 Past Medical History and Family History

Any other medical problems and pregnancy history should also be established. A family history of a bleeding disorder may be useful but a negative family history does not exclude the presence of an IBD, especially if the underlying genetic abnormality has incomplete penetrance or if a *de novo* mutation is present.

1.6.1.2 Medication History

Drug history should also include the use of contraceptive medication, antiplatelet drugs, or other anticoagulants, as this may affect the results of hemostatic assays. Platelet function tests can be affected by high concentrations of alcohol and caffeine and other food (for a list of drugs and food interfering with platelet function see [25]).

1.6.2 Physical Assessment

In addition to a general systemic examination, a number of physical signs may be particularly relevant in the physical assessment

Table 1.1 Bleeding history and salient features indicating non-trivial bleed.

Site of bleeding	Features
Epistaxis	Any nosebleed that causes interference or distress with daily or social activities
Oral cavity	Gum bleeding causing frankly bloody sputum, lasts for 10 minutes or longer on more than one occasion. Tooth eruption or spontaneous tooth loss bleeding that requires assistance or supervision by a physician or lasts at least 10 minutes. Bleeding occurring after bites to lips, cheek, and tongue lasting at least 10 minutes or causing a swollen tongue or mouth
Menorrhagia	Any bleeding that interferes with daily activities such as work, housework, exercise, or social activities during most menstrual periods
Postpartum hemorrhage	Requires medical consultation, supportive treatment
Muscle hematoma	Spontaneous hematoma
Hemarthrosis	Spontaneous bleeding into joint
Cutaneous	Bruises are considered significant when five or more (>1 cm) in exposed areas. Significant features of bruising: (a) atraumatic bruising, (b) bruising occurring at least weekly, and (c) bruises greater than 5 cm
Gastrointestinal bleeding	Bleeding not related to peptic ulcer disease
Surgery	Any bleeding judged by the surgeon to be abnormally prolonged that causes a delay in discharge or requires some supportive treatment
Dental extraction	Any bleeding occurring after leaving the dentist's office and requiring a new, unscheduled visit or prolonged bleeding at the dentist's office causing a delay in the procedure or discharge
Central nervous system bleeding	Subdural or intracerebral hemorrhage

Source: Modified from [18, 19].

of a patient with a bleeding disorder. Careful inspection of the skin, mouth, and nose may reveal bruising or petechiae. Joint examination may reveal swelling or evidence of contractures. Other inherited disorders that cause a bleeding tendency due to a connective tissue disorder, such as Ehlers–Danlos, should also be considered. Signs of a connective tissue disorder may include hypermobility of joints and loose joints. Although occurring very rarely, some inherited platelet disorders may present with other syndromic features such as ocular albinism with late-onset sensorineural deafness.

1.6.3 Investigations

The specificity of bleeding symptoms may be poor and accurate laboratory assessment of the hematological and coagulation system (Table 1.2) is important [7].

A first-line set of investigations includes the full blood count, blood film, and standard coagulation screen (PT, APTT, Clauss fibrinogen, and thrombin time). In the full blood count, it is particularly important to know if the platelet count is within the normal range, elevated or low, as this can help direct further investigations (see Table 1.2). Although the PT and APTT are used widely, they were not designed to be used as screening tools and only assess part of the hemostatic system (see Figure 1.2). If prolonged, they may indicate the presence of an inhibitor or a clotting factor deficiency. An inhibitor could be due to either an antibody that inhibits the activity of a specific clotting factor or a non-specific inhibitor, such as a

Table 1.2 Laboratory assessment of hematological and coagulation system.

Test	Rationale	Possible problem/differential
Full blood count	Is anemia present? This may indicate ongoing bleeding. Look at the mean corpuscular volume (MCV) – if low, this may indicate iron deficiency and/or hemoglobinopathy. Assess platelet count and platelet volume (mean platelet volume)	Anemia Thrombocytopenia or thrombocytosis Large platelets can be associated with inherited platelet disorders such as Bernard–Soulier syndrome (BSS), myosin heavy chain (MYH9)-related disorders or acquired platelet disorders, e.g. immune thrombocytopenia
Blood film	To look at the size and shape of platelets and any other abnormalities present	For example, BSS is a rare autosomal recessive disease associated with bleeding tendency, giant platelets, and thrombocytopenia. MYH9-related disorders are characterized by large platelets and thrombocytopenia
First-line standard coagulation tests		
PT	Prothrombin time	See Figure 1.2
APTT	Activated partial thromboplastin time	See Figure 1.2
Clauss fibrinogen	Assessment of functional fibrinogen	If prolonged, could be due to hypofibrinogenemia, afibrinogenemia, dysfibrinogenemia
Thrombin time (TT)	To assess fibrinogen and presence of heparin	TT prolonged in presence of heparin, direct thrombin inhibitors, fibrinogen disorders
Further tests		
Factor assays	FVIII, IX, XI	Hemophilia A, VWD, hemophilia B, factor XI deficiency
Von Willebrand screen (VWF antigen (Ag) activity (e.g. RiCoF))	To investigate VWD	VWD
Blood group	People with blood group O have 25% lower VWF and FVIII levels	–
Iron studies (ferritin, transferrin saturation, serum iron)	If suspected iron deficiency	Iron deficiency (low ferritin, high transferrin saturation, low serum iron)
More specialized tests		
Light transmission platelet aggregometry	Assessment of platelet function	Abnormalities in aggregometry with Glanzmann's thrombasthenia, BSS, afibrinogenemia, VWD
Others, e.g. TEG, ROTEM, thrombin generation	Global assay of hemostasis	Platelet storage pool disorder, platelet release defect
Other clotting factors, e.g. FXIII, α2 antiplasmin	If the above tests are normal and there is a strong clinical suspicion of an inherited bleeding disorder	FXIII deficiency, α2 antiplasmin deficiency

Table 1.2 (Continued)

Test	Rationale	Possible problem/differential
Genetic mutation analysis	Test if known mutation	For example, VWF mutation
Genomics screen	May be in offered in specialized laboratories	

RiCoF, ristocetin co-factor; ROTEM, rotational thromboelastometry; TEG, thromboelastography; VWD, von Willebrand disease; VWF, von Willebrand factor.

lupus anticoagulant (a lupus anticoagulant is associated with increased risk of thrombosis rather than bleeding). However, a PT or APTT in the normal range does not preclude the diagnosis of a bleeding disorder. They will not pick up platelet defects or mild VWD. Therefore, laboratory results should always be interpreted in light of the clinical history.

If the PT or APTT is prolonged, the next step is to do a mixing study (50:50 mix). Here, normal plasma containing normal levels of clotting factor are mixed with the patient's sample. If, after mixing, there is no correction of the prolonged APTT or PT, this suggests the presence of an inhibitor in the patient's blood. If there is correction, this suggests a factor deficiency and specific factor assays are performed to identify the deficiency.

The Clauss fibrinogen should be measured, rather than the PT-based fibrinogen. The Clauss fibrinogen is a quantitative, functional assay which measures the ability of fibrinogen to form a fibrin clot after being exposed to a high concentration of purified thrombin. For suspected dysfibrinogenemia, there will be a discrepancy between functional activity and antigen level (measured by an enzyme-linked immunosorbent assay (ELISA)-based immunological test). The thrombin time can also be used to assess fibrinogen, although it has mostly been superseded by the Clauss fibrinogen. A prolonged thrombin time may indicate low fibrinogen level (hypofibrinogenemia or afibrinogenemia) and/or abnormal fibrinogen function (dysfibrinogenemia). Thrombin time may also be prolonged if there is heparin present, or if the D-dimers are elevated.

1.6.3.1 Preanalytical Factors in Coagulation Testing

Preanalytical factors are the leading cause of error in coagulation testing [26, 27]. The preanalytical phase describes all actions and aspects of the medical laboratory diagnostic pathway, from when the test is requested up until the analytical phase.

Several preanalytical factors are particularly relevant in women. There have been some reports of lower VWF levels in the first few days of the menstrual cycle. Combined oral contraceptive pills (COCPs) and hormone replacement therapy (HRT) may also affect VWF levels. The elevated VWF levels can mask an underlying VWD [28], although the newer combination OCs (which are of lower dose potency than the estrogen preparations used in the initial case reports) do not appear to have the same effect. Contraceptives can also interfere with other tests of coagulation. They have been reported to lead to increased concentrations of fibrinogen, prothrombin, and factors VII, VIII, and X, and reduction in some coagulation inhibitors [27, 29, 30]. A practical approach would be to test women prior to starting the OC, if possible, but to obtain VWF testing if OCs have already been started. It is also important to consider the effect of pregnancy where factor levels, particularly of VWF, FVIII, and fibrinogen, rise and reach peak levels in the third trimester and continue to be elevated to a lesser degree postpartum.

When performing tests of coagulation, the following factors are important to note and steps should be taken to control for these conditions [26].

- Avoid intense physical exercise for at least 24 hours prior to venepuncture.
- For the diagnosis of VWD in fertile women, blood samples should be obtained on days 1–4 of the menstrual cycle. This may aid in the diagnosis in women with borderline values obtained at other times.
- Test women before starting combined oral contraceptives and HRT if possible.
- For the diagnosis of inherited disorders of hemostasis (particularly VWD and FVIII deficiency), samples should be obtained when normal menstrual cycles have returned or at least two months postpartum. All abnormal values obtained in connection with pregnancy should be verified with repeat blood sampling.
- Avoid long transport times from venepuncture to hemostasis testing. Cold storage of whole blood can lead to artificially low VWF levels.

1.6.3.2 Specialized Tests of Coagulation

Specialized coagulation assays should be performed in a hemostasis laboratory with internal and external quality assurance, in conjunction with other tests of hemostasis and interpreted in light of the clinical history. One of the limitations with current standard coagulation tests is that they look at individual components of the hemostatic pathway. This may be a useful starting point in the diagnostic pathway but they do not give an overall measure of global hemostasis. Tests evaluating global hemostatic capacity (thrombin generation and viscoelastic hemostatic assays, e.g. thromboelastography (TEG) or rotational thromboelastometry (ROTEM)) may provide more accurate evaluation of *in vivo* hemostasis, as they more effectively assess rate/total thrombin generated and whole-blood clot formation. Generally, there seems to be a very poor correlation between laboratory findings and bleeding genotype-phenotype in the rare bleeding disorders such as deficiencies of fibrinogen, prothrombin, FV, combined FV and FVIII, FVII, FX, FXI, and FXIII. TEG and ROTEM show particular promise in the evaluation of hemostasis in patients with rare bleeding disorders where they may be clinically informative [31, 32]. Further work is required for validation in IBDs before widespread clinical use.

Advances in genetic and molecular diagnostics have also been seen in the field of hemostasis. Next-generation sequencing (NGS) has transformed the scale and cost-effectiveness of genetic testing and has emerged as a valuable tool, particularly for the diagnosis of inherited platelet disorders [33]. This is an evolving field and these tests are already becoming more widely available in the diagnostic work-up of an inherited platelet defect (IPD) [1].

1.6.4 Interpretation of Hemostatic Assays

Abnormalities should be interpreted in light of the clinical history and taking into account any preanalytical factors. When assessing low VWF and FVIII levels, it is particularly important to consider whether the patient has blood group O as patients with this blood group have lower levels. Any abnormalities in hemostatic assays should be repeated.

1.7 Summary

The evaluation of bleeding symptoms can be challenging. Definitive diagnosis depends on a unified approach to clinical and laboratory assessment, using objective bleeding assessment tools where possible and considering the potential limitations of tests when interpreting results.

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