Patients with Suspected Inherited and Acquired Bleeding Disorders - Diagnosis - Full Clinical Guideline

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1. Introduction

The guideline below covers the investigation of patients with suspected inherited and acquired bleeding disorders.

2. Aim and Purpose

This document aims to cover the clinical and laboratory assessment of patients with suspected bleeding disorders (inherited and acquired) focussing on:

Haemophilia A & B

In haemophilia A and B, coagulation factors VIII (FVIII) or IX (FIX), respectively, are absent or have deficient function. This impairs the ability of the blood to coagulate leading to increased risk of serious and life-threatening, bleeding which may be delayed.
Both haemophilia A and B are inherited in an X-linked recessive manner and, therefore, almost exclusively males have the phenotype. Homozygosity and lyonisation may lead to haemophilia in females.

Haemophilia A affects approximately 1 in 5000 males, whereas haemophilia B is much less common.

The clinical severity of haemophilia A and B closely correlates with the level of activity of FVIII or FIX, respectively. Severely affected individuals have less than 1 IU/dL activity level in plasma less than 1% of normal); moderately affected 1-5 IU/dL (1-5% of normal); and mildly affected between 5 and 50 IU/dL (5%- 50% of normal).

If inadequately treated, severe haemophilia inevitably will cause spontaneous painful bleeding into joints and muscles. Iron deposition in the cartilage will lead to inflammation and haemophilic arthropathy caused by degeneration of the cartilage and gradual wearing and tearing of bone structure. Serious bleeds also can occur in internal organs, e.g. the brain, with and without trauma or following surgery. Intracranial hemorrhage can have grave consequences, including paralysis and death.

In mild haemophilia abnormal bleeding occurs following operations or trauma, whereas the clinical severity of moderate haemophilia varies from mild to severe. Individuals with FVIII levels less than 0.03 IU/L (less than 3%) usually have a severe phenotype.

When should a diagnosis of haemophilia be suspected?

- A family history of haemophilia is often the reason for referral but 30-50% of new cases have no prior family history.
- When haemophilia is not known in the family, severe haemophilia may be suspected in the following circumstances:
    - abnormal bleeding from the umbilical stump,
    - bleeding following circumcision
    - unusual bruises or hematomas in infant boys (sometimes leading to wrongful suspicion of child abuse)
    - abnormal unexplained bruising or limping in a young boy who has recently started walking

  - Intracranial hemorrhage after birth (including cephalhaematoma) or in infancy

- When no family history is present mild hemophilia may not be diagnosed until adult life. In mild patients trauma and other bleeds may not awake the necessary attention and the outcome may become serious. Female carriers will have symptoms if their levels are low, usually in the mild haemophilia range.
  Reasons to investigate include:
  - Bleeding following a haemostatic challenge such as tooth extraction.
  - Bleeding following surgical intervention or trauma.
  - Unexplained bleeding symptoms in females including post-partum haemorrhage and menorrhagia could be related to low FVIII levels

Screening for haemophilia

General screening assays, i.e. APTT and PT, are important for the initial laboratory evaluation of patients with possible bleeding disorders. If congenital or acquired haemophilia A or B is present the APTT will be prolonged and the PT remains within normal limits. Furthermore, in congenital haemophilia the APTT will be corrected on mixing patient plasma 1:1 with normal plasma. If mixing does not correct the prolongation it may indicate the presence of an inhibitor (or other anticoagulants present in the plasma).

It is important to understand that the APTT is a global plasma assay that depends on the sum effect of 10 different coagulation factors and under certain conditions low FVIII or FIX levels, compatible with mild haemophilia A or B, may be masked by increases of one or several of the other factors resulting in a normal APTT. Upon a possible discrepancy between clinical manifestation/suspicion of haemophilia and screening test results it is recommended to measure FVIII or FIX with factor-specific assays.

Pre analytical variables:

The pre-analytical phase is the time from the blood collection to the point when the sample is analysed in the laboratory. Coagulation tests are exceptionally susceptible to suboptimal sample quality as the sample collection itself will initiate a haemostatic response. Improper sample collection technique and/or incorrect handling prior to analysis will increase the risk of coagulation system activation which may affect the validity of results. This is particularly true for haemophilia testing as FVIII is one of the most labile coagulation factors and is degraded with time in vitro.

Errors and/or delays at the pre-analytical phase can be caused by

- incorrect specimen collection, transportation or storage.
- anticoagulant medication that may interfere with the assay
- an abnormal haematocrit, which may lead to an improper blood to citrate ratio in the test tube.

Sample collection:

The following procedures must be followed to ensure optimal samples are provided for haemostasis testing:

- The tubes should be stored at 4-25ºC and expiry checked on every use.
- Sufficient volume is achieved if blood drawn falls above minimum fill indicator.
- Do not fill above illustrated dashed maximum line.
- Any samples filled below the fill indicator line will be rejected as insufficient.
- Allow the tube to fill until the vacuum is exhausted and blood flow ceases.
- A discard tube (without additives) must be used if only a citrate tube is to be drawn using a winged blood collection set. It is important to remove the air from the blood collection set to ensure the proper blood volume is obtained in the tube.
- Do not fill tubes from other tubes or combine two partially filled citrate tubes.
- Immediately after draw, gently invert tube 3 to 4 times. Do not shake.
- A visual check should be performed on the sample prior to patient departure and any uncertain fill levels addressed at the time to avoid the patient attending for a repeat.
- Transport to the laboratory promptly at room temperature.
- Centrifuge within 1 hour of phlebotomy to obtain platelet poor plasma

FVIII and FIX assays general points

Plasma FVIII:C or FIX:C level represents the functional (coagulation) activity of the factors and can be measured using either coagulation-based or chromogenic assays.

The FVIII:C and FIX:C assays are calibrated with material that has traceability to the current international standard for FVIII or FIX in plasma. In this way the result is given in international units (IU) and one IU is the factor activity present in one mL normal plasma. In RDH currently the result is given in IU/dL, which is the same as percentage in absolute numbers. (Some laboratories use IU/mL which may cause confusion).

Factor VIII assays

Two factor VIII assays are available at RDH**:** a *one-stage assay* and a *chromogenic assay.*

Assay discrepancy

The different FVIII:C assays should give similar result in most cases. However, patients with certain mutations in the FVIII gene causing mild haemophilia A may be missed using the one-stage APTT based FVIII assay. In some cases the one-stage assay result may be several times higher than the chromogenic assay. In general, the results of the chromogenic reflect the clinical phenotype in hemophilia A better compared with the one-stage assay. There are also some genotypes causing inverse assay discrepancy, with lower one-stage than chromogenic assay results in mild haemophilia A. These individuals may have normal chromogenic results which correlates with a normal bleeding phenotype.

Thus, mild haemophilia A may be challenging to identify correctly in the laboratory, if only one of the assay principles are used.

Factor IX assays

The one-stage assay is used at RHD.

Laboratory testing for diagnosis

- Individuals with a suspected bleeding disorder and a prolonged APTT should have all intrinsic pathway factor assays performed (FVIII, FIX, FXI and FXII)

- All new cases with suspected haemophilia A should have both one-stage and chromogenic assays FVIII assays in order to ensure correct classification of severity.
- Performing a chromogenic FVIII level should be considered in an individual with a significant bleeding history but normal APTT to rule out mild haemophilia with discrepant levels.
- As FVIII is an acute phase reactant and rises in other situations such as pregnancy and stress, repeat testing may be needed in individuals who have borderline results.

Genetic testing:

Genetic diagnosis is clinically useful to predict the risk of inhibitor formation and for carrier and prenatal diagnosis.

Before any laboratory genetic testing can be undertaken, counselling should be offered by professionals with appropriate training in counselling and specialist experience in heritable bleeding disorders. These counsellors should also work in close association with local clinical genetic services. Counselling and appropriate antenatal investigations and care should be offered to carriers and potential carriers of haemophilia. All individuals undergoing genetic testing should give written consent using the UKHCDO Information on Genetic Testing and Consent Form for patients and families with bleeding, thombotic and/or platelet disorders.

All children with haemophilia should have their genotype established as soon as possible after diagnosis.

It is recommended that severe haemophiliacs should be screened for the F8 intron 22 inversion mutation followed by the F8 intron 1 inversion mutation. This approach should identify the underlying mutation in 45-50% of severe haemophilia A patients.

The remaining severe haemophilia A pedigrees should then be analysed further by full mutation analysis of F8.

Moderate and mild haemophilia A is not associated with a common mutational mechanism and patients require full mutation analysis.

All genetic testing at Royal Derby Hospital is sent to Manchester.

Von Willebrand's Disease guideline

Von Willebrand disease (VWD) is a bleeding disorder caused by deficiency of Von Willebrand factor (VWF). VWD is usually inherited, but rare acquired VW can occur.

Congenital VWD is divided into:
'Low VW' and type 1 VW, both characterized by quantitative deficiency of VWF (type 1 VW has VW levels less than 30%)

Type 2 VW characterized by qualitative deficiency of VWF. Type 2 is further subdivided into subtypes 2A, 2B, 2M and 2N, depending on the type of functional disorder.

Type 3 characterized by total lack of VWF and therefore also has a very low FVIII level.

Table 1 Types of von Willebrand disease

Type	Description
1	**Partial quantitative deficiency of VWF**
2	**Qualitative VWF defect**
2A	**Decreased VWF-dependent platelet adhesion with a selective deficiency of high molecular weight multimers**
2B	**Increased affinity for platelet GPIb**
2M	**Decreased VWF-dependent platelet adhesion without a selective deficiency of high molecular weight multimers**
2N	**Markedly decreased binding affinity for factor VIII**
3	**Virtually complete deficiency of VWF**

When should a diagnosis of VWD be suspected:

The major clinical hallmark in VWD is a tendency to mucocutanoeus bleeding and any patient presenting with symptoms suggestive of a primary haemostatic defect should be investigated for Von Willebrand's disease.

Bleeding histories can however be subjective and there is considerable overlap between symptoms suffered by patients with VWD and the normal population. It is hence recommended that bleeding scores such as the Bleeding Assessment Tool developed by the ISTH should be

used to standardise history taking and to improve decisions regarding the significance of bleeding symptoms.

Laboratory testing for VWD diagnosis and classification

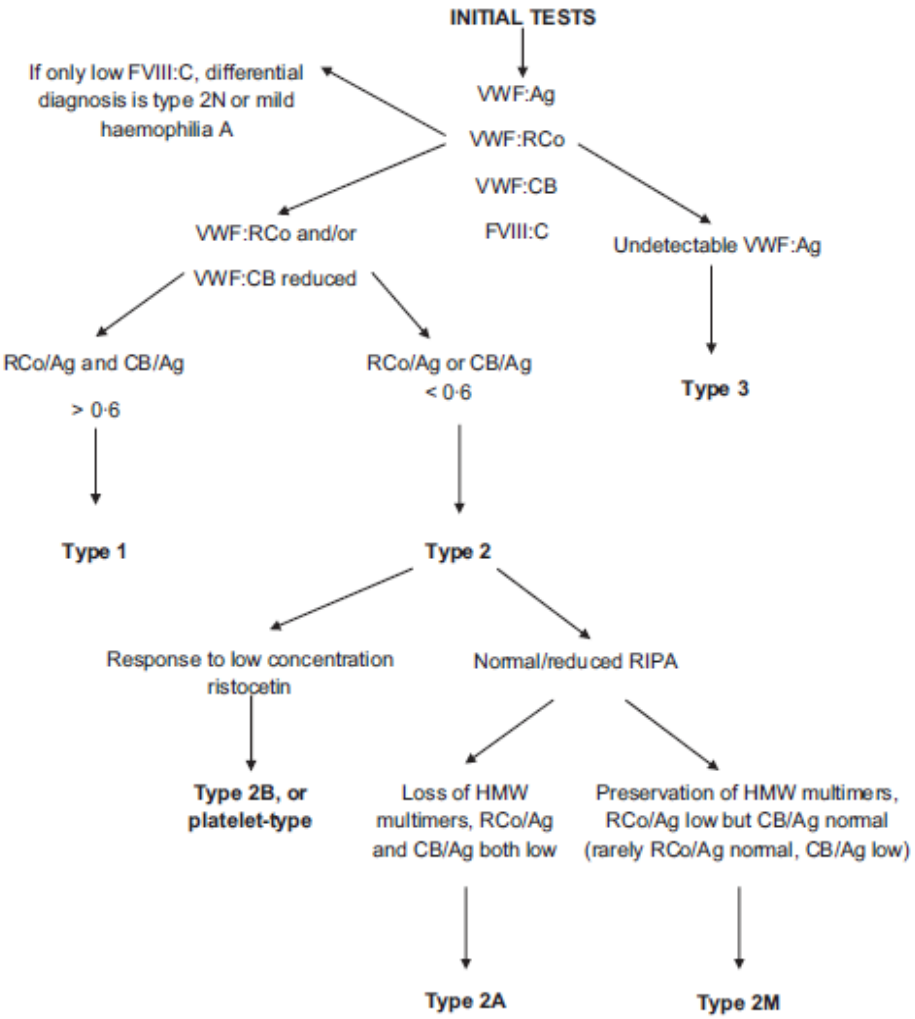
The following laboratory tests are required for the initial diagnosis and classification of VWD. It is important to note that a normal APTT does not exclude a diagnosis of VWD.

Method	Diagnostic and classification purpose
VIII assay	Determination of factor VIII coagulation activity
VWF: Ag	Concentration of the VWF Antigen
VWF Activity VWF:RCo VWF:CB	 The main functional VWF method. Measures the ability of the VWF to bind to GPIb and cause agglutination of normal platelets An activity assay dependent on the presence of HMW multimers and an intact collagen binding site
Multimer Analysis	Should not be performed until a diagnosis of VWD is made. Multimeric analysis was essential for the strict classification of type 2 VWD. See below.
Ristocetin induced platelet aggregation (RIPA)	Diagnosis of type 2B by detection of heightened sensitivity to ristocetin
VWF:FVIII binding assay	Determines the capacity of VWF to bind FVIII. Mutations in binding site can give rise to 2N VWD.

In the initial investigation for VWD, VIII assay, VWF:Ag and VWF: RCo is measured.

A function: Ag ratio of < 0.6 is used to identify patients with type 2 VWD. Multimer analysis can be used to distinguish between types 2A and 2M. Genetic testing has largely replaced Multimer analysis.

The following diagnostic algorithm adapted from BCSH guidelines on VWD is used for classification of VWD



Genetic analysis and family testing:
Genetic analysis is undertaken under the following circumstances as per BCSH guidelines:

- To distinguish between type 2B VWD and platelet type VWD
- To distinguish between 2N VWD and mild or moderate haemophilia
- Prenatal diagnosis of type 3 VWD
- For cases where above tests do not accurately clarify the VWD subtype

Before any laboratory genetic testing can be undertaken, counselling should be offered by professionals with appropriate training in counselling and specialist experience in heritable bleeding disorders. These counsellors should also work in close association with local clinical genetic services. Counselling and appropriate antenatal investigations and care should be offered to carriers and potential carriers of haemophilia. All individuals undergoing genetic testing should give written consent using the UKHCDO Information on Genetic Testing and Consent Form for patients and families with bleeding, thombotic and/or platelet disorders.

Family testing

When a diagnosis of VWD is made it is appropriate to test first degree relatives with or without a positive bleeding history. In this circumstance, a presumptive diagnosis of VWD may be made on the basis of laboratory findings alone.

Genetic testing for all patients at the Royal Derby hospital is sent to Manchester.

Acquired haemophilia guideline

Acquired haemophilia (AH) is a severe bleeding disorder caused by inhibiting autoantibodies against a coagulation factor, most often factor (F) VIII, developing in a patient with no previous history of bleeding.

It is a rare disorder with an incidence of about 1-2/million per year. Mostly elderly persons are affected with the exception of the rare occurrence in females postpartum. The APTT is prolonged but other laboratory screening tests for haemostasis like platelet count and prothrombin time are normal. Patients with AH represent a demanding clinical challenge. The morbidity and mortality are quite high, and treatment involves the use of specific and expensive coagulation promoting products. The diagnosis requires identification of autoantibodies (inhibitors) with specialised laboratory tests.

When should a diagnosis of AH be suspected:

An acquired inhibitor should be considered in patients with recent onset of abnormal bleeding. Patients usually present to clinicians with limited experience of the disorder and diagnosis and appropriate treatment is often delayed. Massive bleeds may occur after intravenous venepuncture if special care is not taken. Severe and life-threatening bleeding is common in AHA, although, in contrast no haemostatic treatment is required in 25–33%
of cases and some patients present without clinical bleeding.

The clinical features of AHA differ from those of congenital haemophilia because bruising, retroperitoneal, muscle, gastrointestinal and urogenital bleeding are common whereas haemarthroses are uncommon.

Laboratory screening methods:

- APTT is prolonged
- Prothrombin time assays (including the INR) are normal

- Platelet and leukocyte counts are generally normal. The haemoglobin value may be low due to bleeds

Before proceeding with further investigations, exclude treatment with anticoagulants and check lupus anticoagulant.

Blood sampling for further testing:

- Blood samples are drawn in 5 mL vacutainer tubes containing 0.5 mL 3.2-3.8 % (0.11-0.13 M) trisodium citrate.
- The tubes must be filled and immediately turned 5-10 times for even mixing of blood and citrate.
- The tubes should be centrifuged within 30 minutes after blood sampling at 2000 g during 20 minutes.
- The plasma is removed from the blood cells and tested immediately (or frozen if unable to do so)

Further tests:

Mixing studies:

Patient plasma is mixed with an equal volume of pooled normal plasma and incubated for 1-2 h at 37°C. Typical laboratory findings in AH are of abnormal coagulation screening tests that do not correct with normal plasma, either with an immediate or incubated mix.

Factor assays:
Determination of FVIII:C (If the factor VIII is normal do VW levels).

Inhibitor assay (Antibodies to FVIII (or other coagulation factors)):
The inhibitor titre is expressed in Bethesda units (BU). One Bethesda Unit is defined as the quantity of antibody, which reduces the FVIII activity by half in normal plasma when patient plasma is mixed with an equal volume of normal plasma for 2 h at 37°C. The Nijmegen modification is used to improve assay sensitivity.

All the above tests are undertaken locally at the Royal Derby Hospital.

Inherited Platelet disorders:

Inherited platelet function disorders are a wide spectrum of qualitative platelet disorders with variable bleeding tendency, ranging from mild bleeding to severe life-threatening episodes. Diagnosis and classification of inherited platelet function disorders is a challenge.

When should a diagnosis of inherited platelet disorders be suspected:

Patients with platelet disorders may present with thrombocytopenia incidentally on a screening complete blood count or with bleeding manifestations consistent with platelet-type bleeding: mucocutaneous bleeding, gastrointestinal bleeding, menorrhagia, and postsurgical or traumatic bleeding.

Diagnosing inherited platelet function disorders:

Assessment of patients with suspected inherited platelet function disorder requires objective clinical assessment of bleeding history, any family history and physical examination followed, when appropriate, by laboratory investigations. During this process it is essential to recognize that numerical and/or functional platelet disorders are prevalent amongst patients with abnormal bleeding and may be clinically indistinguishable from other haemostatic disorders, particularly von Willebrand disease (VWD). Laboratory investigations of platelet number and function are therefore recommended in any patient where bleeding symptoms are not fully explained by standard clinical laboratory investigations.

At the Royal Derby hospital, laboratory investigations available for platelet function testing include tests to assess the platelet numbers and size (full blood count and film) as well as the PFA 200 which is a screening tool to measure global haemostatic platelet function. Patients requiring platelet function testing by light transmission aggregometry are referred to Birmingham for further assessment.

Specimen collection for PFA 200

Venepuncture.

Ideally, samples for platelet function studies should only be collected from fasting and resting subjects who have refrained from smoking and caffeine ingestion on the day of testing. If the patient is taking medication known to affect platelet function, e.g. non-steroidal anti-inflammatory drugs testing should, if possible, be deferred for 10–14d after the last dose.

The following sampling recommendations must be adhered to for optimal results:

- A complete record of current medication taken by patients or controls should be taken prior to blood collection to either prevent unwanted drug interference or help interpretation of test results
- Collect blood using a standardized, atraumatic protocol, with minimal stasis
- Use needles between 19 and 21 gauge; evacuated tube systems or syringes are acceptable (2C).
- The first 3–5ml of blood should not be used for platelet function tests
- Use 105–109mmol/l buffered trisodium citrate tubes
- Maintain specimens at RT
- Keep tubes upright and capped; do not subject to excessive mixing or agitation; do not use pneumatic transport systems
- Samples should be tested between 30 min and no more than 4h from blood collection.

Genetic screening for patients:

Patients suspected to have inherited platelet disorders from the above testing will be referred to Birmingham or Nottingham for full platelet function aggregometry testing and further genetic screening as required.

Before any laboratory genetic testing can be undertaken, counselling should be offered by professionals with appropriate training in counselling and specialist experience in heritable bleeding disorders. These counsellors should also work in close association with local clinical genetic services. Counselling and appropriate antenatal investigations and care should be offered to carriers and potential carriers of haemophilia. All individuals undergoing genetic testing should give written consent using the UKHCDO Information on Genetic Testing and Consent Form for patients and families with bleeding, thombotic and/or platelet disorders.

Rare inherited clotting disorders diagnosis guideline

Overview:

Rare inherited bleeding disorders are a heterogeneous group of coagulation disorders characterized by fibrinogen, prothrombin, factors V, VII, X, XI, or XIII (FV, FVII, FX, FXI, or FXIII, respectively), and the combined factor V + VIII and vitamin K–dependent proteins deficiencies,

representing roughly 5% of all bleeding disorders. They are usually transmitted as autosomal, recessive disorders, and the prevalence of the severe forms could range from 1 case in 500 000 for FVII up to 1 in 2-3 million for FXIII in the general population. Patients affected with RBDs may present a wide range of clinical symptoms, varying from mucocutaneous bleeding, common to all types of RBDs to the most life-threatening symptoms such as central nervous system and gastrointestinal bleeding.

Diagnosis of these disorders must be suspected in any patient presenting with symptoms of mucocutaneous bleeding and in patients with unexplained prolongation of the PT and/or the APTT.

Fibrinogen deficiency:

Fibrinogen deficiency is an autosomal recessive or dominant disorder in which quantitative (afibrinogenaemia or hypofibrinogenaemia) or qualitative (dysfibrinogenaemia) defects in the fibrinogen protein chains lead to reduced functional fibrinogen.

When should the diagnosis be suspected?

The most common symptoms are mucocutaneous, soft tissue, joint, genitourinary, traumatic and surgical bleeding. Umbilical stump bleeding may be a presenting feature. Arterial and venous thrombosis, poor wound healing and splenic rupture are rare features of afibrinogenaemia and hypofibrinogenaemia. Diagnosis should be excluded in patients with unexplained prolongation of PT and APTT.

Laboratory testing:

- APTT and PT are prolonged
- Prolonged thrombin clotting time
- Absent or reduced fibrinogen activity measured using the Clauss fibrinogen assay
- Fibrinogen Ag assay (send to Nottingham) can distinguish between a/hypo and dysfibrinogenaemia.

Prothrombin deficiency

Prothrombin (FII) deficiency is an autosomal recessive disorder in which reduced plasma prothrombin activity is caused by quantitative (hypoprothrominaemia) or qualitative (dysprothrombinaemia) defects in the FII protein. FIID has an estimated prevalence of one in 2 000 000.

Clinical features:

The most common features are mucocutaneous, soft tissue, joint and surgical bleeding. Diagnosis should be excluded when there is unexplained prolongation of the PT and APTT.

Laboratory tests:

- Prolonged PT and APTT
- Mixing studies show full correction with normal plasma in heritable Factor II deficiency
- Reduced factor II activity by one stage PT-based assay

Factor V Deficiency

Factor V (FV) deficiency is an autosomal recessive disorder in which reduced plasma FV activity is caused by quantitative or, very rarely, qualitative defects in the FV protein. F5D has an estimated prevalence of one in 1 000 000.

Clinical features:

The most common features are mucocutaneous, soft tissue, joint and surgical bleeding. Diagnosis should be excluded when there is unexplained prolongation of the PT and APTT.

Laboratory testing:

- Prolonged PT and APTT
- Reduced FV activity determined by the one stage PT based assay

Factor VII deficiency:

Factor VII (FVII) deficiency (F7D; MIM #227500) is an autosomal recessive disorder in which reduced plasma FVII activity is caused by quantitative or qualitative defects in theFVII protein. F7D has an estimated worldwide prevalence of one in 500 000 (Mannucci et al, 2004).

Clinical features:
The most common features are mucocutaneous, soft tissue, joint and surgical bleeding. Diagnosis should be excluded in patients with unexplained isolated prolonged PT.

Laboratory tests:

- Prolonged PT
- APTT is normal
- Reduced factor VII activity by a 1-stage PT based assay.

Factor X deficiency

Factor X (FX) deficiency is an autosomal recessive disorder in which reduced plasma FX activity is caused by quantitative or qualitative defects in the FX protein. F10D has an estimated worldwide prevalence of one in 1 000 000.

Clinical features:

The most common features are mucocutaneous, soft tissue, joint and surgical bleeding.

Laboratory tests:

- PT and APTT are both prolonged
- Reduced factory X activity measured by a one stage PT based assay

Factor XI deficiency

Factor XI (FXI) deficiency is an autosomal recessive or dominant disorder in which reduced plasma FXI activity is caused by quantitative or, very rarely, by qualitative defects in the FXI protein.

Clinical features:

About 65% of patients with factor XI deficiency are asymptomatic and the diagnosis is picked up during investigations for a prolonged APTT. The patients that are symptomatic usually present with symptoms of bleeding after surgery and trauma.

Laboratory features:

- Usually presents as an isolated prolonged APTT

- Reduced Factor XI levels determined by a one stage APTT based assay.

Factor XIII deficiency

Factor XIII (FXIII) deficiency is an autosomal recessive disorder in which reduced plasma FXIII activity is caused by quantitative or, rarely, by qualitative defects in the FXIII A-subunit protein. F13D has an estimated worldwide prevalence of one in 2 000 000.

Clinical features:

The most common features are soft tissue, umbilical, surgical, joint and intracranial bleeding.

Laboratory features:

- Normal PT/APTT and Thrombin time
- Reduced plasma Factor XIII activity using the ammonia release assay

Genetic testing:

Any patients requiring genetic testing will have samples sent to Manchchester.

References

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4. Documentation Controls

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