Inherited bleeding disorders

Vickie McDonald

Steven K Austin

Abstract

The most common inherited disorders of coagulation are von Willebrand disease (VWD), haemophilia A and haemophilia B. Haemophilia A and B are sex-linked disorders, whereas VWD is inherited in an autosomal fashion. Definitive diagnosis is made using coagulation factor assays after a thorough history and examination. Treatment of bleeding episodes is with therapies that, where possible, avoid the use of blood products, to reduce the hypothetical (but possible) risk of transfusion-transmitted infection. Recombinant factors VIII and IX are the products of choice for haemophilia A and B, respectively, but recombinant von Willebrand factor (VWF) concentrate is awaiting regulatory body approval for use. Target factor concentrations for surgery and to treat bleeding are 100%. Inhibitors can develop with factor VIII and IX therapy; bypassing agents are then required to treat bleeding. Desmopressin (DDAVP) increases endogenous VWF concentration and, in addition to tranexamic acid, is often used in type 1/2 VWD before surgery or to treat bleeding. Other coagulation factor deficiencies are rare, with specific concentrates for most conditions. Inherited platelet disorders are thought to be very rare. Milder forms are usually managed with tranexamic acid or DDAVP, but more severe forms require platelet transfusions and/or recombinant factor VIIa.

Keywords Bleeding; coagulation factors; DDAVP; factor replacement; haemophilia; platelets; von Willebrand

Key points

- Many inherited bleeding disorders are less common than acquired ones
- The most common inherited bleeding disorder is von Willebrand disease
- Milder forms of inherited bleeding disorders can present later in life, but more severe forms present in childhood
- Treatment involves replacement with factor concentrate (or plasma where no concentrate is available), but novel therapies are emerging
- Patients with haemophilia who are given factor concentrate can develop an inhibitor to the replacement factor, making it ineffective in managing bleeding
- Congenital platelet disorders are often diagnosed owing to the complexity of platelet assays, but are actually rare

Introduction

Inherited disorders of coagulation, although less common than acquired abnormalities, are life-long conditions. Severe disorders usually present in childhood, but milder forms may not be clinically apparent until later in life when patients have haemostatic challenges. Definitive diagnosis should be made at a centre with clinical and laboratory expertise.

Diagnosing congenital bleeding disorders

Patients are usually referred either to investigate abnormal bleeding or because of a family history of an inherited bleeding disorder. The approach should be systematic and include a full clinical history, examination and investigations.

History

Important facts to note from the history include the patient's gender, the frequency and type of bleeding (e.g. muscle and joint bleeding, mucocutaneous bleeding, unexplained bleeding after surgical challenges) or simple bruising. An extended family history is very important to track the inheritance of these disorders.

Examination

Bruises may be larger than expected and occur with minimal trauma and in atypical sites such as the trunk. Examine the mucosal surfaces such as the skin, mouth and joints for bruises, petechiae and signs of bleeding.

Investigations

The initial tests that should be performed are as follows:

- Full blood count and blood film (for platelet abnormalities).
- Coagulation screen – prothrombin time (PT), activated partial thromboplastin time (APTT) and Clauss fibrinogen; 50/50 mixing tests with normal plasma and incubation studies should be performed if the APTT or PT is prolonged, to ensure no inhibitors are present. In 50/50 mixing tests, the patient's plasma is mixed with an equal volume of normal plasma. If coagulation factor deficiencies are present, the APTT or PT correct to normal, but if an inhibitor is present in the patient's plasma, they remain abnormal.

More specialized tests can be used to diagnose the specific disorder, as follows:

Vickie McDonald *MA PhD MRCP FRCPath is a Consultant Haematologist at Guy's and St Thomas' NHS Foundation Trust, UK. Competing interests: none declared.*

Steven K Austin *MB BS (Hons) BMedSci FRACP FRCPA is a Consultant Haematologist at Guy's and St Thomas' NHS Foundation Trust, and Director of the Haemophilia Centre at St George's University Hospitals NHS Foundation Trust, London, UK. Competing interests: none declared.*

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- Clotting factor/von Willebrand factor (VWF) assays — if the PT is prolonged, test factors II, VII, V and X; and if the APTT is prolonged, test factors VIII, IX, XI and XII (NB: factor XII deficiency does not lead to bleeding.).
- Platelet function tests — the PFA-100 is a quick screening test that is abnormal in platelet function disorders and VWD but has low specificity. Formal platelet aggregation studies are required to diagnose platelet function defects more specifically.[1]

In general, patients with congenital bleeding disorders should not be given antiplatelet agents, anticoagulants such as heparin or intramuscular injections.

von Willebrand disease (VWD)

This is the most common inherited bleeding disorder. There are three main types of VWD:[2] type 1 is a partial quantitative defect with autosomal dominant inheritance and accounts for about 70% of cases; type 2 is a qualitative defect with autosomal dominant or recessive inheritance; and type 3 is a severe quantitative defect with autosomal recessive inheritance.

Clinical features

Bleeding severity usually correlates with the factor concentration. Bruising and mucocutaneous bleeding such as or/trauma. Joint bleeds are rare.

Laboratory investigation[2]

The APTT is prolonged, although milder forms of VWD can have a normal coagulation screen. In quantitative abnormalities of VWF, VWF antigen and activity assays are reduced in proportion to each other. Additional tests for qualitative defects include VWF multimer analysis and collagen binding. Patients with type 2B VWD (qualitative defect) have associated thrombocytopenia. Blood group O is associated with lower concentrations of VWF than other blood groups and rarely contributes to a bleeding phenotype. Therefore the patient's blood group should be taken into consideration when diagnosing VWD.

Clinical manifestations and treatment of haemophilia A and B

Factor concentration (% normal)	Age of onset	Symptoms	Treatment
<1% = severe haemophilia	<1 year	Can have intracranial bleed at birth Spontaneous bleeding into joints and muscles is common Bleeding after: • Surgery • Dental extraction • Trauma	Factor VIII or IX concentrate for acute bleeds, cover for surgery and invasive procedures Factor VIII or IX concentrate prophylaxis in children and some adults to prevent bleeds Tranexamic acid also given as adjunctive therapy
1–5% = moderate haemophilia (moderate disease)	Can have later onset of symptoms than severe form, but still present in childhood	Occasional spontaneous bleeding; bleeding after surgery, dental extraction and trauma	Treatment: some patients need regular factor VIII or IX concentrate; factor VIII or IX replacement to treat bleeds and cover surgery or invasive procedures Tranexamic acid is an adjuvant/alternative therapy
6–40% = mild haemophilia	Variable onset and may not present until adulthood	Bleeding after surgery, dental work and trauma	Regular factor VIII or IX prophylaxis usually not required but factor replacement required for treatment of bleeding or prevention for surgery/invasive procedures. Some patients with haemophilia A respond to desmopressin rather than factor concentrate Tranexamic acid is an adjuvant/alternative therapy

Dose calculation for factor replacement: Dose (units/kg) = [(desired concentration − current concentration) × body weight]/IVR. IVR (*in vivo* recovery) = 2 for haemophilia A, 1 for haemophilia B.

Table 1

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