Bleeding Disorders

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Bleeding Disorders

Vascular bleeding disorders

- Heterogeneous group of conditions characterized by easy bruising and spontaneous bleeding from the small vessels.
- The underlying abnormality is either in the vessels themselves or in the perivascular connective tissues.
- Coagulation tests are normal.

Inherited vascular disorders

- Hereditary haemorrhagic telangiectasia

AD, Rare.

- Connective tissue disorders

In the Ehlers–Danlos syndromes there are hereditary collagen abnormalities with purpura resulting from defective platelet adhesion.

Acquired vascular defects

Congenital Coagulation Disorders

1) haemophilia A (factor VIII)
2) haemophilia B (factor IX)
3) VWD

Hemophilia A

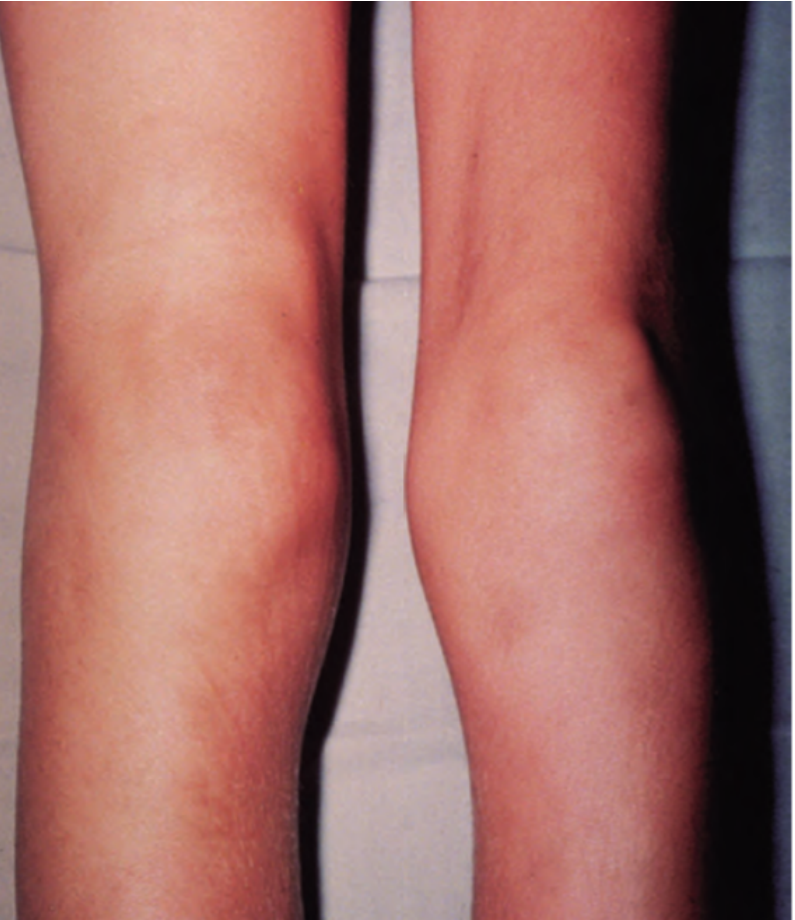
- Deficiency of factor VIII results from an abnormality in the factor VIII gene, which lies at the the long arm of the X-chromosome.
- Ranging form single-point mutations to large deletions.
- The prevalence of this disorder is about one per 10 000 males.
- Females with haemophilia have been observed extremely rarely and these are either homozygotes for the abnormal gene or are heterozygotes in whom the normal X-chromosome has not produced sufficient quantities of factor VIII due to lyonization.
- In the plasma, factor VIII is only found complexed with VWF, which acts as a carrier and prolongs its plasma half-life.

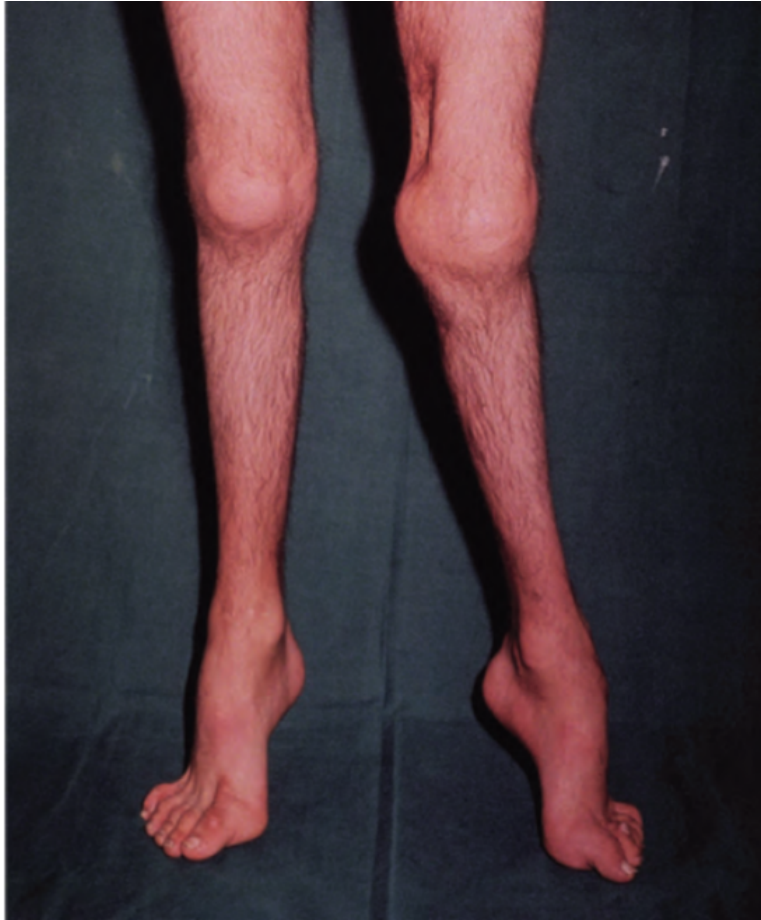
Hemophilia A

- Prenatal diagnosis of haemophilia can be made by analysis of fetal DNA, which can be obtained either by chorionic villus sampling between 11 ½ and 14 weeks of gestation or by amniocentesis after 16 weeks.
- Genetic mutational analysis allows carriers to be identified with accuracy and is the method of choice.

Clinical features

- Infants may develop profuse post-circumcision haemorrhage or joint and soft tissue bleeds and excessive bruising.
- Recurrent painful haemarthroses and muscle haematomas dominate the clinical course of severely affected patients
- If inadequately treated, lead to progressive joint deformity and disability.
- Intracranial bleeding is the most common cause of death from the disease itself.





Diagnosis

- The possibility of haemophilia is suggested by the finding of a normal PT and a prolonged APTT.
- Confirmation is by a specific assay of factor VIII coagulant activity with normal VWF.

Correlation of coagulation factor activity and disease severity in haemophilia A or B
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Coagulation factor activity (percentage of normal)	Clinical manifestations
<1	Severe disease Frequent spontaneous bleeding into joints, muscles, internal organs from early life Joint deformity and crippling if not adequately prevented or treated
1–5	Moderate disease Bleeding after minor trauma Occasional spontaneous episodes
>5	Mild disease Bleeding only after significant trauma, surgery

Treatment

- Treatment should be given at the earliest sign of spontaneous or post-traumatic bleeding.
- Treatment consists of intravenous injections of factor VIII concentrate.
- Guidelines exist for the plasma level to be achieved for different types of haemorrhage.
- A controlled trial has proven that regular prophylaxis is far superior to on- demand treatment.
- Approximately 25% of patients with haemophilia, usually after treatment with factor VIII on 10-20 occasions, develop antibodies that inhibit its functional activity.

Treatment

- Haemorrhage in patients with high-titre inhibitors may require treatment with ‘bypassing agents’ such as recombinant factor VIIa or FEIBA (factor eight inhibitor bypassing activity; that is, a plasma-derived activated prothrombin complex concentrate), which activate the coagulation cascade below the level of factor VIII.
- The administration of factor VIII may be avoided in mild to moderate haemophilia by using the vasopressin analogue desmopressin (DDAVP), which causes a temporary increase in factor VIII and VWF by provoking the release of these factors from endothelial cells. DDAVP is used intravenously, subcutaneously or intranasally.

Haemophilia B (Factor IX deficiency, Christmas disease)

- The clinical features and inheritance of factor IX deficiency are identical to those in factor VIII deficiency.
- Factor IX deficiency affects about 1 in every 50 000 males.
- The factor IX gene is located on the long arm of the X-chromosome.
- The APTT is prolonged and the PT normal. The diagnosis can be made by assay of the factor IX level.
- Plasma-derived factor IX concentrate or recombinant factor IX is available and should be administered intravenously as soon as spontaneous or post-traumatic bleeding starts.
- Factor IX has a longer half-life in the plasma (18-24 hours) than factor VIII and hence can be given at less frequent intervals.

Von Willebrand disease

It is an autosomal disorder characterized by mild, moderate or severe bleeding.

- VWF has two function:
  - binds platelets to subendothelial tissues.
  - It acts as a carrier for factor VIII.

The most common inherited bleeding disorder withprevalence of up to 1%

Most mild cases are undiagnosed.

The bleeding results from either a qualitative abnormality or a quantitative deficiency of VWF.

The reduction in VWF results in a reduction in factor VIII concentration (can be misdiagnosed as hemophilia A).

VWD

- VWD has been divided into three types:
  Types 1 (most frequent) partial reduction, AD
  Type 3 there is nearly complete absence of VWF molecules, AR
  Type 2 there are qualitative abnormalities, AD or AR

  Spontaneous bleeding is usually confined to mucous membranes and skin most commonly epistaxes and ecchymoses.

  Bleeding into joints and muscles is rare except in type 3 disease.

Diagnosis

- The laboratory findings include:
  - Prolonged PFA closure time.
  - Usually a prolonged APTT.
  - Reduced factor VIII clotting activity
  - Reduced levels of VWF antigen or activity.
  - Impaired ristocetin-induced platelet aggregation.

Treatment

For type 1 disease, desmopressin (DDAVP) is the first line treatment.
DDAVP increases plasma levels of both VWF and factor VIII.
Very high purity VWF concentrate may be used.
The antifibrinolytic drug (tranexamic acid) may be used for treating epistaxis or menorrhagia.

Deficiency of other clotting factors

Acquired bleeding disorders

- Liver disease.
- Vitamin K deficiency
- DIC
- Acquired hemophilia.
- Drugs (heparin, warfarin, tPA, rivaroxaban, dabigatran)

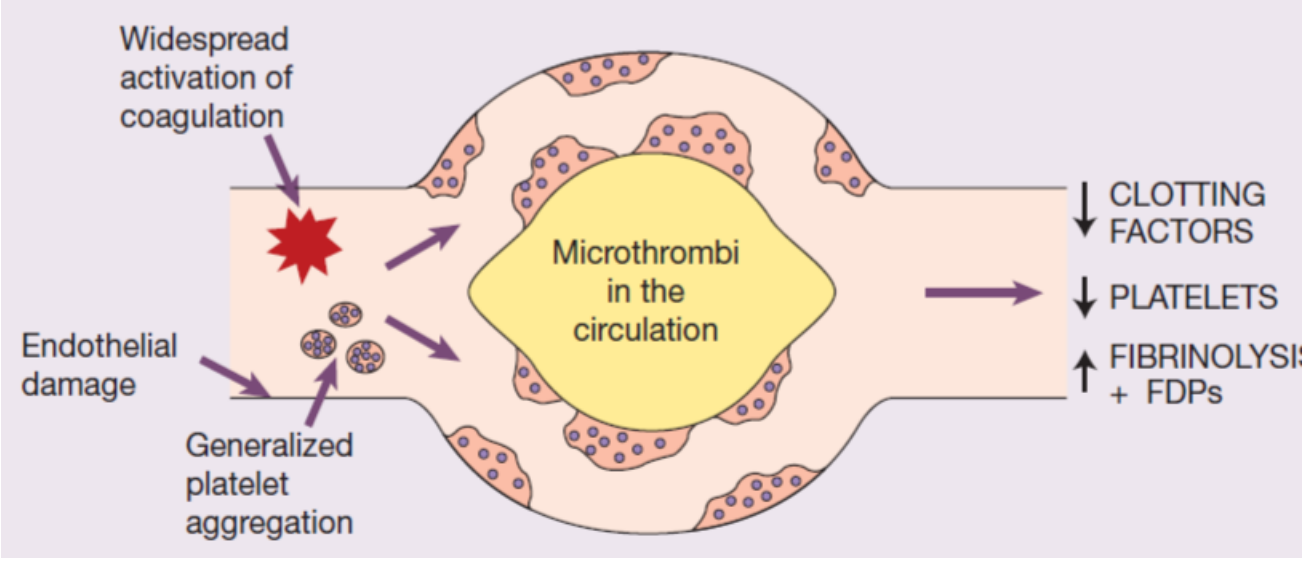
Vitamin K Deficiency

- Fat-soluble obtained from green vegetables and bacterial synthesis in the gut.
- Hemorrhagic disease of the newborn:
  - Caused by liver cell immaturity, lack of gut bacterial synthesis of the vitamin and low quantities in breast milk.
  - usually on the second to fourth day of life, but occasionally during the first 2 months.
  - PT and APTT are both prolonged.

Disseminated intravascular coagulation (DIC)

- Generalized activation of the clotting system followed by marked activation of the fibrinolytic system.
- Acute DIC may be associated many serious/lifethreatening diseases.
- Clotting cascade is activated in various ways(tissue damage, collagen exposure, release of TF and other procoagulants)
- Activation of the cascade leads to the generation and dissemination of large amounts of thrombin in the circulation, the activation of platelets and the formation of intravascular microthrombi.
- As a consequence of the fibrin formation, the fibrinolytic mechanism is activated, resulting in high concentrations of FDPs, including D-dimers.

DIC


Widespread activation of coagulation
Endothelial damage
Generalized platelet aggregation
Microthrombi in the circulation
CLOTTING FACTORS
PLATELETS
FIBRINOLYSIS + FDPs

Causes of DIC

Infections Gram- negative and meningococcal septicaemia Clostridium welchii septicaemia Severe falciparum malaria Viral infection – varicella, HIV, hepatitis, cytomegalovirus	Malignancy Widespread mucin- secreting adenocarcinoma Acute promyelocytic leukaemia	Obstetric complications Amniotic fluid embolism Premature separation of placenta Eclampsia; retained placenta Septic abortion
Hypersensitivity reactions Anaphylaxis Incompatible blood transfusion	Widespread tissue damage Following surgery or trauma. After severe burns	Vascular abnormalities Kasabach–Merritt syndrome Leaking prosthetic valves Cardiac bypass surgery Vascular aneurysms
Miscellaneous Liver failure Pancreatitis Snake and invertebrate venoms Hypothermia Heat stroke Acute hypoxia Massive blood loss		

DIC

- The haemorrhagic manifestations may be so severe in acute DIC as to lead to death
- In chronic DIC, the haemorrhagic tendency may be mild or moderate.
- Some patients with chronic DIC are asymptomatic because the activation of the clotting and fibrinolytic systems is finely balanced and the production of clotting factors and platelets is sufficiently increased to compensate for their increased consumption.

Diagnosis

1 The platelet count is low.

2 Fibrinogen concentration is low.

3 High levels of fibrin degradation products (D- dimers).

4 The PT and APTT are prolonged.

5 RBCs fragments in blood smear.

Compensation by the liver may render some of the coagulation

tests normal.

Treatment

- Treatment is aimed at preventing further coagulation by removal of the initiating cause.
- Supported with transfusions of blood, fresh-frozen plasma and platelet concentrates in order to restore blood volume and replace clotting factors and platelets.

Acquired hemophilia

- Acquired hemophilia is a rare but life-threatening condition
- Caused by the development of autoantibodies (inhibitors) directed against plasma coagulation factors, most frequently factor VIII (FVIII).
- Could be idiopathic or secondary to underlying condition (autoimmune disease, infection, malignancy,…)
- More common in the elderly
- Treated with ‘bypassing agents’ such as recombinant factor VIIa or

FEIBA and immune suppression.

Massive transfusion syndrome

- Blood loss results in reduced levels of platelets, coagulation factors and inhibitors.
- Further dilution of these factors occurs during replacement with red cells.
- Some protocols include 1 : 1 : 1 for red cells, platelet packs and FFP