Hematology

438 teamwork

Bleeding disorders [1]

Color index:
Red: Important
Gray: Extra, notes

Editing file

Introduction to Vascular Bleeding disorders

Definition: Heterogeneous (different) group of conditions characterized by easy **bruising** and spontaneous **bleeding** from the small vessels. With **normal coagulation tests.** Usually the underlying abnormality is either in the **vessels** themselves or in the **perivascular** connective tissues.

Causes of bleeding disorders:

- **Vascular disorders, Thrombocytopenia, Defective platelet function, Defective coagulation.**

Vascular defects

Acquired vascular defects

- **Simple easy bruising** (in young healthy women with unknown cause) is a common benign disorder which occurs in otherwise healthy women, especially those of child-bearing age.
- **Senile purpura** caused by atrophy of the supporting tissues of cutaneous blood vessels. The most common acquired vascular defect Seen in old adults (Considered normal)
- **Henoch-schönlein purpura** is usually seen in children and often follows an acute upper respiratory tract infection.

Inherited vascular defects

- **Hereditary hemorrhagic telangiectasia** [2]**:** Autosomal dominant , Rare.
- **Connective tissue disorders e.g.:**
  -Ehlers–Danlos syndrome [3]**:** There are hereditary **collagen abnormalities,** with purpura resulting from defective platelet adhesion.

Bleeding disorders

Bleeding disorders

Acquired bleeding disorders

1- **Liver disease.**
2- **Vitamin K deficiency**
3- **DIC**
4- **Acquired hemophilia.**
5- **Drugs (heparin, warfarin, tPA, rivaroxaban, dabigatran)**

Congenital/ Inherited bleeding disorders
(coagulation or clotting factor disorders)

1- **Haemophilia A (factor VIII)** A looks like ^ so its factor ^ deficiency.
2- **Haemophilia B (factor IX)** B for **benign** so it is factor 9 deficiency.
3- **Von Willebrand disease**

NOTE: Single deficiencies of factors other than VIII and IX are rare. **All factors deficiency** give rise to bleeding disorders of varying degrees of severity, **except contact factor** (plasma kallikrein-kinin system) **(e.g. factor XII and** XI, and plasma prekallikrein (PK)**)**

Haemophilia A

inherited in an X-linked recessive pattern

Definition: **Deficiency of factor VIII** results from a mutation in the factor VIII gene, which lies at the the **long arm of the X-chromosome**. It ranges form **single-point mutations to large deletions.**

1

- 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** [4] **for the abnormal gene** or are **heterozygotes** in whom the normal X-chromosome has **not produced sufficient quantities of factor VIII** due to lyonization [5].

2

Prenatal diagnosis of haemophilia can be made by analysis of fetal DNA, which can be obtained either by chorionic villus sampling between 11.5 and 14 weeks of gestation or by amniocentesis after 16 weeks.

3

In the plasma, **factor VIII is only found complexed with VWF**, which acts as a carrier and prolongs its plasma half-life.

4

Genetic mutational analysis allows carriers to be identified with accuracy and is the method of choice.

Haemophilia A cont.

Clinical features:

01 Infants may develop **profuse post-circumcision haemorrhage** or **joint and soft tissue bleeds** and excessive bruising.

02 Recurrent painful **hemarthrosis** and **muscle haematomas** dominate the clinical course of severely affected patients

03 If inadequately treated, lead to **progressive joint deformity** and disability.

04 **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**.

Treatment

- Treatment should be given at the earliest sign of spontaneous or post-traumatic bleeding, which 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.
- 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) inherited in an X-linked recessive pattern

Characteristics:

01 The **clinical features** and inheritance of factor IX deficiency are **identical to those in factor VIII deficiency.**

02 The factor IX gene is located on the **long arm of the X-chromosome.**

03 Factor IX deficiency affects about **1 in every 50 000 males.**

04 The **APTT is prolonged** and the **PT normal.** The diagnosis can be made by **assay of the factor IX level.**

05 **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.

06 **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.

Correlation of coagulation factor activity and disease severity in haemophilia A or B

Coagulation factor activity (percentage of normal)	Clinical manifestations
<1	• Severe disease with 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.

Von Willebrand disease

Definition: It is an **autosomal disorder** characterized by mild(most are undiagnosed), moderate or severe bleeding. The bleeding results from either a **qualitative** abnormality or a **quantitative deficiency of VWF**. It's the most common inherited bleeding disorder with prevalence of up to 1%.

What are the functions of VWF?

- Binds platelets to subendothelial tissues.
- It acts as a carrier for factor VIII.

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

Types of VWD

- Spontaneous bleeding is usually confined to mucous membranes and skin most commonly epistaxis and ecchymoses.
- Bleeding into joints and muscles is rare **except in type 3 disease.**

Type 1 (most frequent): partial reduction, AD (Autosomal dominant)

Type 2: There are qualitative abnormalities, AD or AR (Autosomal recessive)

Type 3: There is nearly complete absence of VWF molecules, AR

Diagnosis

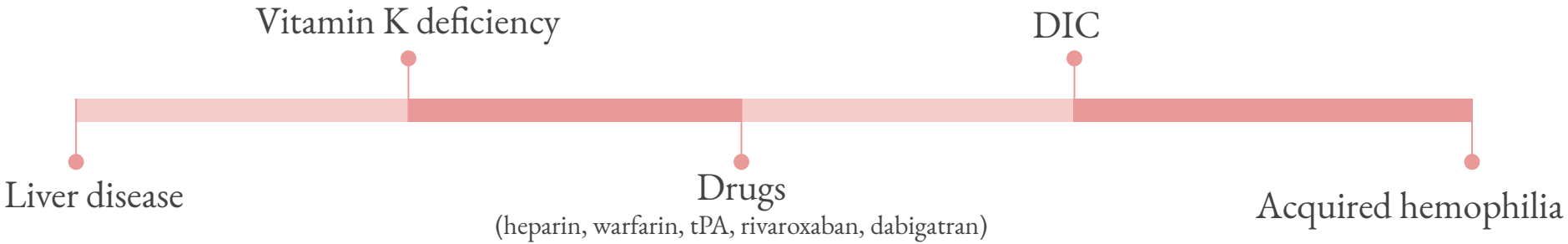
The laboratory findings include:

- **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.

Acquired bleeding disorders



Vitamin K deficiency

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


liver cell immaturity


lack of gut bacterial synthesis of the vitamin


low quantities in breast milk

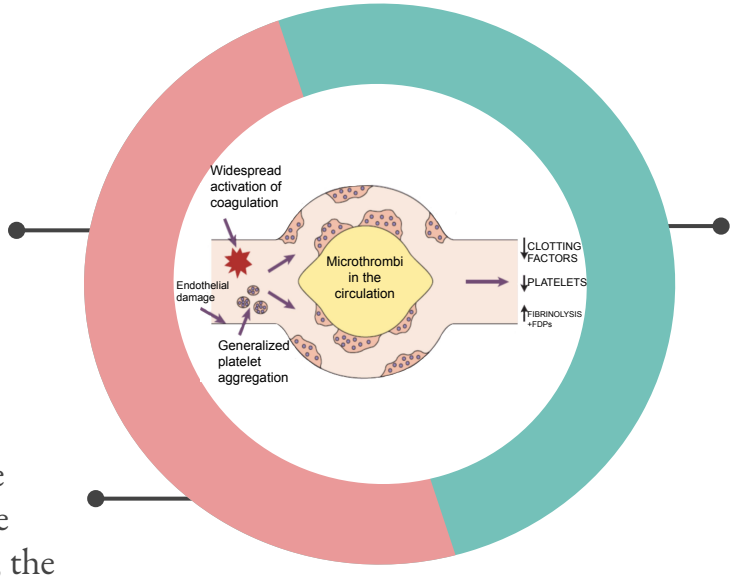
Disseminated intravascular coagulation (DIC)

- Generalized activation of the clotting system followed by marked activation of the fibrinolytic system
- Acute DIC may be associated many serious/lifethreatening diseases

Clotting system

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



Fibrinolytic system

As a consequence of the fibrin formation, the fibrinolytic mechanism is activated, resulting in high concentrations of FDPs, including D-dimers

Causes of DIC

01:

Infections

-Gram-negative
-meningococcal septicaemia
-Clostridium welchii septicaemia
-Severe falciparum malaria

Viral infection:
-varicella
-HIV
-hepatitis
-cytomegalovirus

02:

Malignancy

Widespread mucin-secreting adenocarcinoma

Acute promyelocytic leukaemia

03:

Obstetric

Obstetric complications
Amniotic fluid embolism
Premature separation of placenta
Eclampsia; retained placenta
Septic abortion

04:

Hypersensitivity

- Anaphylaxis

-Incompatible blood transfusion

05:

Mechanical

Widespread tissue damage
Following surgery or trauma.
After severe burns

06:

Vascular

-Vascular abnormalities
Kasabach–Merritt syndrome
-Leaking prosthetic valves
-Cardiac bypass surgery
-Vascular aneurysms

07:

Miscellaneous

-Liver failure
-Pancreatitis
-Snake and invertebrate venoms
-Hypothermia
-Heat stroke
-Acute hypoxia
-Massive blood loss

Clinical manifestation of DIC

Acute DIC

- The haemorrhagic manifestations may be so severe as to lead to death

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

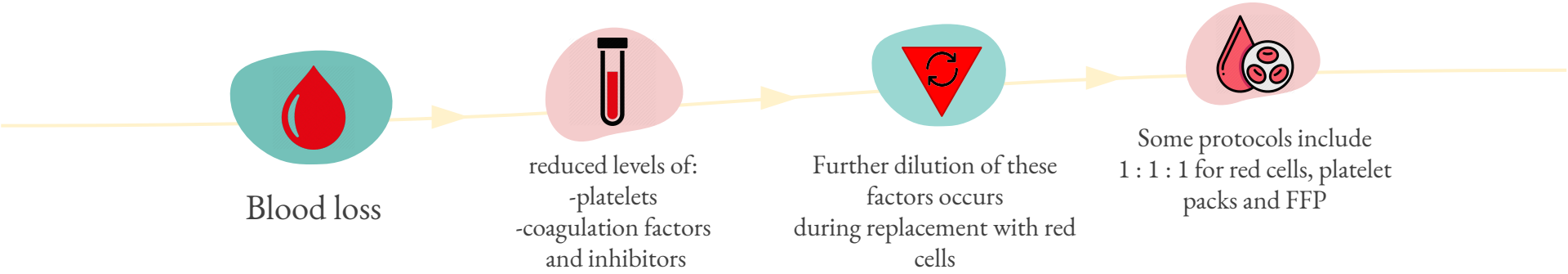
Treatment is aimed at preventing further coagulation by removal of the initiating cause

Supported with transfusions of blood, fresh-frozen plasma and platelet concentrates in order to restore blood volume and replace clotting factors and platelets.

Acquired haemophilia

- 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



1-**The cause of bleeding disorders is one of these defects:** a-vascular disorder, b-thrombocytopenia, c-problems in platelet function or d-coagulation factors (most common cause).
2-this disease leads to abnormal blood vessel formation in the skin, mucous membranes, and often in organs such as the lungs, liver, and brain. Telangiectasias are small dilated blood vessels that can occur near the surface of the skin or mucous membranes.
3-since collagen is abnormal in this disease , when injury happens platelets wouldn't be able to bind to this abnormal collagen.
4-an individual having two identical alleles of a particular gene or genes and so breeding true for the corresponding characteristic.
5-is a process by which one of the copies of the X chromosome is inactivated in female mammals (In this case the normal X is inactivated)

Dr. Notes

1-Bleeding is more commonly caused by Acquired vascular defects
2-In platelets defect we will have: mucocutaneous hemorrhage,
In coagulation cascade defect we will have: deep joint and deep tissue hemorrhage
3-Prolonged thrombin time is only seen in:
A- patient taking heparin
B- defected fibrinogen
4-Normal Coagulation factor activity of factor VIII is about 55
5-Hemophilia B is less common than Hemophilia A

Quiz

Key answers:
1-D 2-C 3-D 4-A 5-B 6-B

1-Hemophilia B caused by deficiency of factor:

A. VI
B. VII
C. VIII
D. IX

2-Factor VIII is found complexed with :

A. Factor IX
B. Albumin
C. VWF
D. Factor X

3-Which of these findings is related with hemophilia A?

A. Shortened APTT
B. Decreased PT
C. Increased PT
D. Prolonged APTT

4-The complete absence of VWF is seen in:

A. Type 3 VWD
B. Type 2 VWD
C. Type 1 VWD
D. None

5-Where is factor IX gene located?

A. Short arm of chromosome X
B. Long arm of chromosome X
C. In both arms of chromosome X
D. Has no specific locus

6-The most frequentlY factor involved in Acquired hemophilia is:

A. VII
B. VIII
C. IV
D. X

THANKS

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