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haematology Team

MED 443 King Saud University

Bleeding disorder

GNT Block

COLOR INDEX:

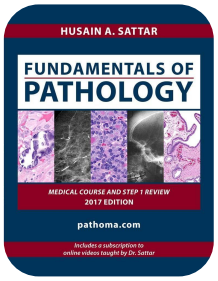
- Main text
- Dr. Notes
- Male's text
- Femal's text
- Important
- Extra

Editing file:

Objectives

*No objectives were found in both male and female slides

Click on PATHOMA for a revision and more info!



Our YouTube's playlist for this lecture!

This lecture was given by: Dr.Osamah T.Khajoh and prof. Fatma Al Qahtani

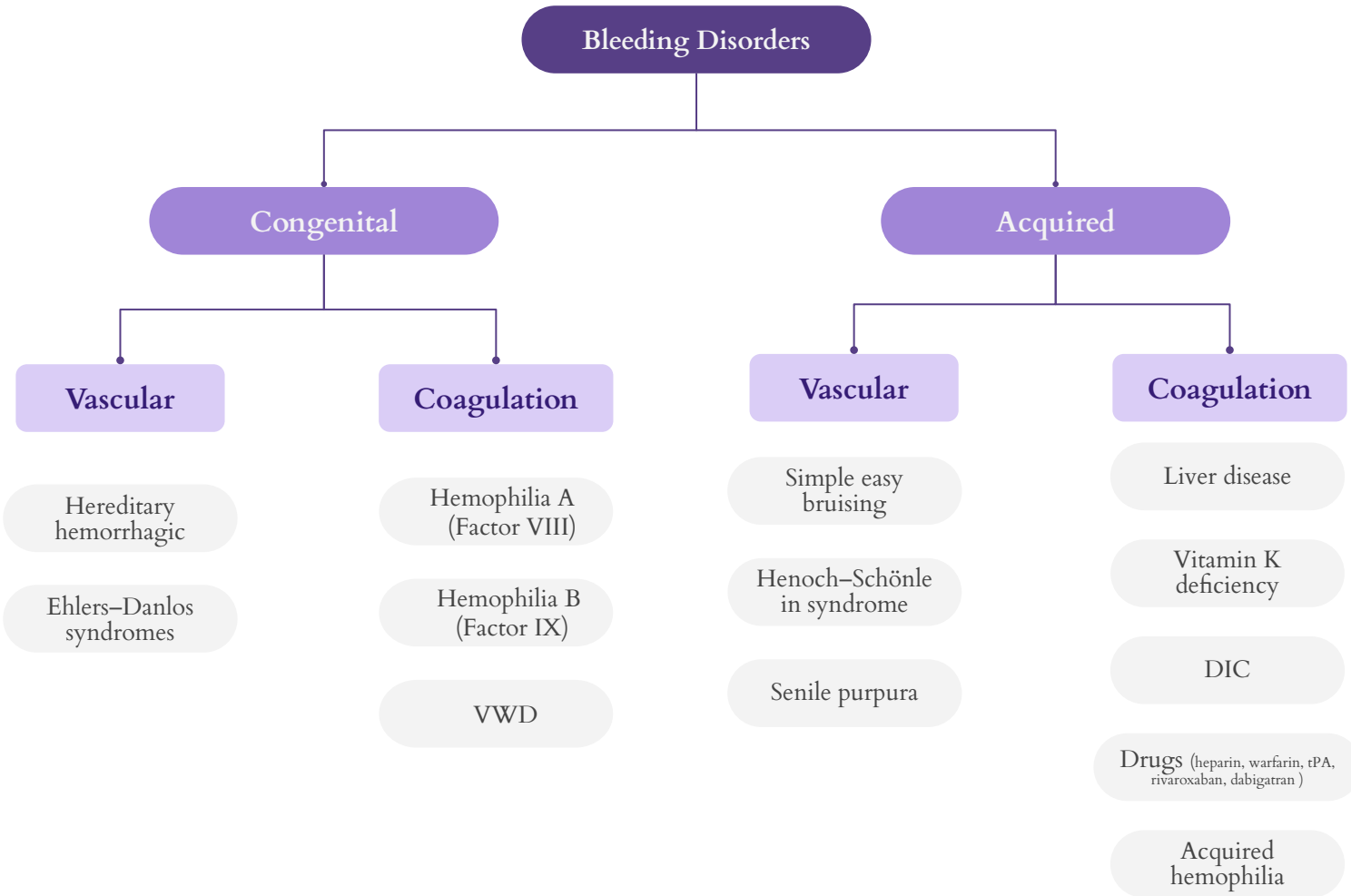
EXTRA

Overview

Bleeding disorders can results from:

1. Vascular Disorders
2. Defective Platelet Function
3. Thrombocytopenia
4. Defective Coagulation

Clinical differences between diseases of platelets/vessel wall and of coagulation factors.		
Type	Platelets/vessel wall disease	Coagulation diseases
Mucosal bleeding	Common	Rare
Petechiae	Common	Rare
Deep haematomas	Rare	Characteristic
Bleeding from skin cuts	Persistent	Minimal
Sex of patient	Equal	>80% male



Bleeding Disorders

Bleeding disorders result from: problems in the count or function

- Vascular Disorders
- Thrombocytopenia
- Defective Platelet Function
- Defective Coagulation

Vascular Bleeding Disorders

- Vascular Bleeding Disorders are Heterogeneous group of conditions.
- Characterized by **easy bruising and spontaneous bleeding** from the **small vessels.**
- The underlying abnormality is either:

1- In the vessels themselves.
2- In the perivascular connective tissues.

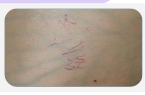
- **Coagulation tests are normal.** Characterised by that

Vascular bleeding disorders are divided into:

Inherited Vascular Disorders

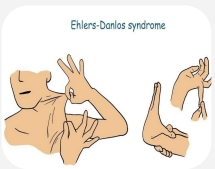
Hereditary hemorrhagic telangiectasia

AD(Autosomal dominant), Rare.



Connective Tissue Disorders

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

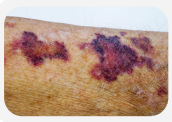


Acquired Vascular Defects

Simple easy bruising

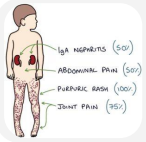
Is a common benign disorder which occurs in otherwise healthy women, especially **those of child-bearing age.**

Senile purpura in old people: hands are bluish



caused by **atrophy** of the supporting tissues of نزيف تحت الجلد cutaneous blood vessels

The Henoch–Schönlein syndrome



is usually seen in children and often follows an acute upper respiratory tract infection

Congenital Coagulation Disorders

Congenital Coagulation Disorders

Most common in paediatric, نادر عند الكبار

1. Hemophilia A (Factor VIII)
2. Hemophilia B (Factor IX)
3. VWD

Hemophilia A:

Overview

- 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.more common in male
- **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. So it's not free in plasma.

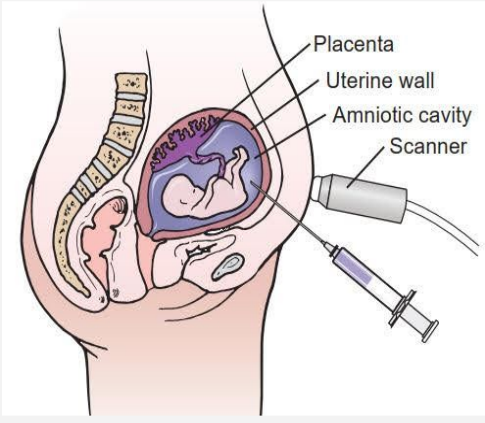
This means that deficiency of VWF could cause secondary Hemophilia A because VWF is a carrier for factor VIII

Males Dr note: It's not important

Prenatal diagnosis of haemophilia can be made by analysis of fetal DNA, which can be obtained either:

1-by **chorionic villus** sampling between 11 ½ and 14 weeks of gestation or
2-by **amniocentesis** after 16 weeks.

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



Congenital Coagulation Disorders

Hemophilia A:

Clinical Features

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

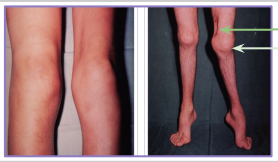
Recurrent painful hemarthrosis (Bleeding into a joint: important characteristics of haemophilia)**and muscle haematomas** dominate the clinical course of severely affected patients

If inadequately treated, lead to progressive

joint deformity and **disability**, Muscle wasting

In both types of hemophilia there are: Intramuscular or intra-joint bleeding

There is abnormal joint and feet



Intracranial bleeding is the most common cause of death from the disease itself.

Diagnosis

1. Screening test
   The possibility of haemophilia is suggested by the finding of a normal PT(because its related to intrinsic pathway so its normal)and a **prolonged APTT.**

2. Confirmation is by a specific assay of factor VIII coagulant activity with normal VWF.

IMPORTANT

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

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

Congenital Coagulation Disorders

Hemophilia A:

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.**

من كثر مأخذ Factor VIII

- Haemorrhage in **patients with high-titre inhibitors** may require treatment with **'bypassing agents'** such as:
  1- recombinant factor VIIa (to increase the activity of the cascade)
  2- 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)best treatment for mild to moderate haemophilia , 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.**

Congenital Coagulation Disorders

Hemophilia B (Factor IX deficiency, Christmas disease):

Overview

- 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.Less prevalence than hemophilia A
- The factor IX gene is located on the long arm of the **X-chromosome.**

Diagnosis

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

Treatment

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.

Congenital Coagulation Disorders

Von Willebrand Disease "VWD":

Overview

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

functions of Von Willebrand Factor (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)

VWD has been divided into three types:

Type 1

- most frequent
- **partial** reduction
- AD(Autosomal dominant)
- Quantitative abnormalities

Type 2

- there are **qualitative abnormalities**
- AD or AR(Autosomal recessive)

Type 3

- there is nearly **complete absence** of VWF molecules
- AR
- Quantitative abnormalities

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.
because there might be a reduction in factor VIII

Males Dr note:
important Clinical finding to differentiate between hemophilia A (bleeding in major big joint) and VWD(epistaxis)

Diagnosis

The laboratory findings include:

- **Prolonged PFA closure time.**Platelet function assay
- **Usually a prolonged APTT.**
- Reduced factor VIII clotting activity
- Reduced levels of VWF antigen or activity.
- Impaired ristocetin-induced **platelet aggregation.** specific to type 2

Congenital Coagulation Disorders

Von Willebrand Disease "VWD":

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.

Comparison EXTRA

	Hemophilia A	Hemophilia B	VWD
Cause	factor VIII deficiency	Factor IX deficiency	Von Willebrand Factor deficiency
Inheritance	Sex-linked (X-chromosome)		Dominant (incomplete)
Prevalence	1 per 10 000 males.	1 in every 50,000 males.	1 per 100 The most common
Main sites of haemorrhage	Muscle, **joints**, post-trauma or postoperative		**Mucous membranes**, skin cuts, post-trauma or postoperative
PT	Normal		
APTT	Prolong		
PFA-100	Normal		Prolong

Which test is used to differentiate between **vWD** & **hemophilia A?**
Platelet aggregation test

Deficiency of other clotting factors

- Single deficiencies of factors other than VIII and IX are rare.
- All factors deficiency except **contact factor (e.g. factor XII)** give rise to bleeding disorders of varying degrees of severity. **factor XII deficiency will give raise to thrombotic event**

Acquired Bleeding Disorders

Acquired bleeding Disorders

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

Vitamin K Deficiency:

Fat-soluble obtained from green vegetables and bacterial synthesis in the gut.(Needed for factor II, VII, IX , X)

Hemorrhagic disease of the <u>newborn</u>:

- Caused by
  - **a.** liver cell immaturity
  - **b.** lack of gut bacterial synthesis of the vitamin
  - **c.** low quantities in breast milk. Early delivery
- usually on the **second to fourth day of life**, but occasionally during the first 2 months.

PT and **APTT** are both prolonged.why they are both prolonged? because Vit K is essential for both intrinsic and extrinsic pathways

Disseminated intravascular coagulation (DIC):

Generalized <u>activation</u> of the **clotting system** <u>followed</u> by marked activation of the **fibrinolytic system.**

Acute DIC may be associated many **serious/life threatening diseases.**

Acquired Bleeding Disorders

Disseminated intravascular coagulation (DIC):

Pathogenesis

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.** Abnormal Activation

As a consequence of the **fibrin formation**

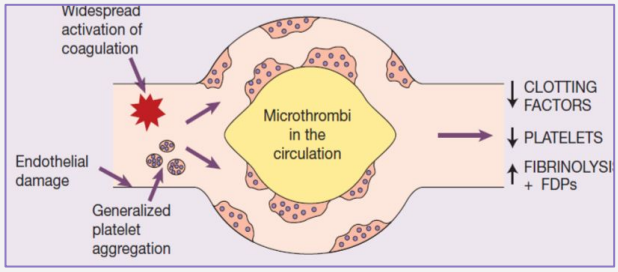
The **fibrinolytic mechanism** is activated

Resulting in

Very high in circulation

high concentrations of **FDPs**, including **D-dimers.**

D-dimers: a protein fragment (small piece) that's made when a blood clot dissolves in your body.



Causes of DIC

Read it. but you need to understand it

Miscellaneous	Infections	Obstetric complications
• Liver failure • Pancreatitis • Snake and invertebrate • venoms • Hypothermia • Heat stroke • Acute hypoxia • Massive blood loss	• Gram-negative and meningococcal septicaemia • Clostridium welchii septicaemia • Severe falciparum malaria • Viral infection – varicella, HIV, hepatitis, cytomegalovirus	• Amniotic fluid embolism • Premature separation of placenta • Eclampsia; retained placenta • **Septic abortion**
Hypersensitivity reactions:	**Malignancy**	**Widespread tissue damage**
• Anaphylaxis • Incompatible blood transfusion	• Widespread mucin-secreting adenocarcinoma **Acute promyelocytic leukaemia** M3	• Following surgery or trauma • After severe burns

Vascular abnormalities

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

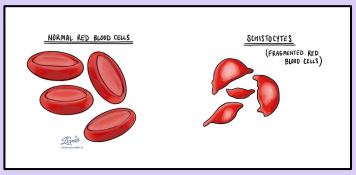
Acquired Bleeding Disorders

Disseminated intravascular coagulation (DIC):

Diagnosis

- **Fibrinogen** concentration is low.
- **The platelet** count is low,
- **thrombocytopenia**, due to high consumption

- RBCs fragments in blood smear (Schistocytes)



High levels of fibrin degradation products (D-dimer), that correlates with activity of coagulation and fibrinolysis

- PT and APTT are prolonged.

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.

Types of DIC

Acute	Chronic
The haemorrhagic manifestations may be so **severe in acute DIC as to lead to death**. • Acute DIC may be associated many serious/life threatening diseases.	**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.

Acquired Bleeding Disorders

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:

Very rare

- **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

Test result		Causes of test result pattern EXTRA
PT	aPTT	
Normal	Prolonged	Deficiency of factor VIII, IX, or XI
		von Willebrand disease (variable)
Prolonged	Prolonged	Liver disease
		DIC
		Severe vitamin K deficiency

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