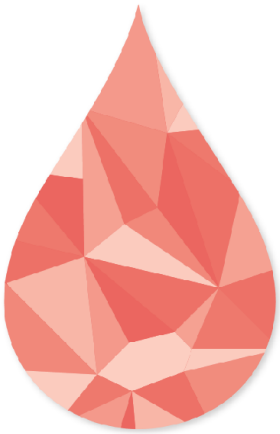


12-bleeding disorders.

= Haematology 435 =

إن أحسنا فمن الله عزوجل, وإن أخطأنا فمن أنفسنا والشيطان.
نظراً لشمولية العمل لمحاضرات الطلاب والطالبات بإمكانكم اعتماده كمصدر للمذاكرة

❖ Learning objectives:

- to know the main sequence of events in the coagulation pathways.
- To know the principles underlying the PT, APTT, and TT (thrombin time).
- To know the principles of investigation of patient suspected of having a haemostatic defect.
- To know the mode of inheritance, clinical presentation , method of diagnosis and principles of treatment of hemophilia A,B ,C and vWD.
- To know the alternations in the hemostatic and fibrinilytic mechanisms associated with DIC and the causes of DIC..
- To understand normal fibrinolysis and the principles of fibrinolytic therapy.

➢ Color Codes:

- Pink: Girls' notes. Blue: Boys' notes. Red: Important Notes. Gray: Extra notes.
- Purple: Lecture notes & Pathoma notes.

➢ References:

- Girls&Boys Doctors Slides and Notes.
- Lecture notes pathology (chapter 12)
- Pathoma (chapter 5)
- Team 434 & 433.

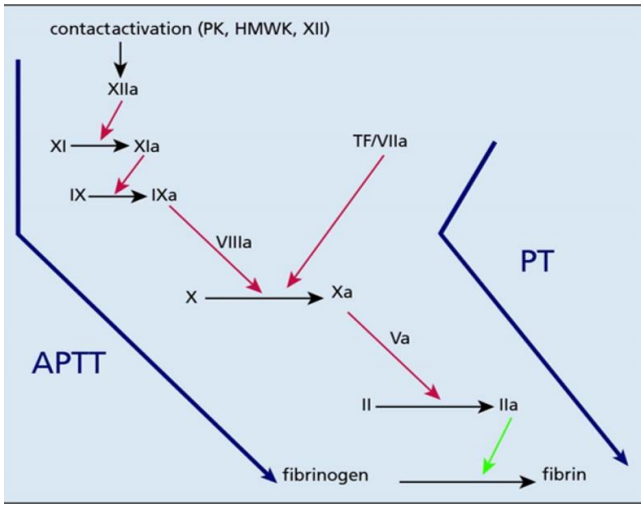
Revised by
خولة العماري & هشام الغفيلي

➢ Correction File: (HERE)

تتذكروا ال disorders of secondary hemostasis اللي بالمحاضرة الرابعة اللي سببها ال coagulation factors؟ بهذي المحاضرة بتكلم عن ال disorders هذي.

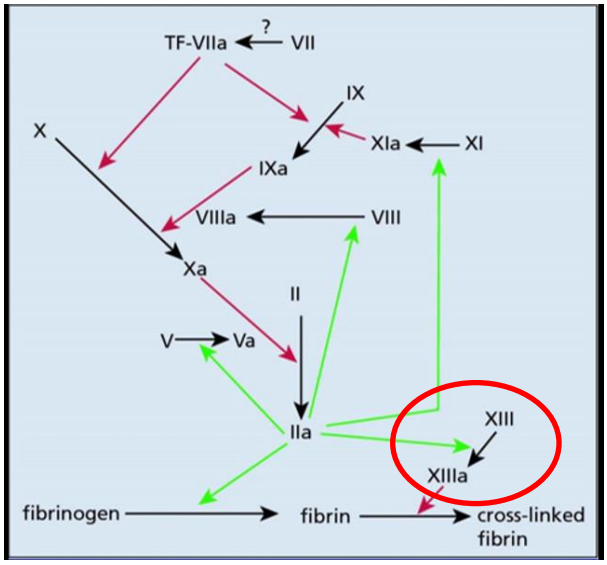
❖ Normal coagulation mechanism: نفس الشي موجود بالفيسيولوجي أقرأووه كأنه مراجعة

Coagulation cascade: Video.



-The pathway on the left is called the **"intrinsic pathway"** why? because all the factors we need in this pathway are in the blood, which are **factors XII,XI and IX.** Any deficiency in the factors of this pathway will lead **prolonged APTT test** (activated partial thromboplastin time).
-The pathway on the right side is called the **"extrinsic pathway"** why? Because all the factors in this pathway are found outside the blood (these factors are: **tissue factor "TF" and factor VII),** any deficiency in of any of these factors will lead to **prolonged PT test** (prothrombin time).
-Any deficiency in any of the factors in the **common pathway (X,V,II and I "fibrinogen")** will lead to prolonged time in **both PT and APTT.**

All the coagulation factors are directly involved in the coagulation cascade, **EXCEPT** coagulation factor number XIII (Factor XIII or fibrin stabilizing factor, it crosslink the fibrin and stabilize it).
Deficiency of this factor (FXIIID) affects clot stability (poor healing).



❖ So, what are the tests for clotting factors:

1-The activated partial thromboplastin time (APTT).

2-The Prothrombin time (PT)

3-The thrombin time (measures fibrinogen) **how?** We add thrombin to the patients plasma and we measure the time taken to clot.

thrombin time is prolonged when there's an inherited or acquired deficiency of fibrinogen or in abnormal fibrinogen (dysfibrinogenemia) "we have fibrinogen but it's not functioning" or in the presence of heparin or raised levels of FDPs (fibrinogen degradation products).

We have congenital and acquired coagulation disorders:

	Congenital	Acquired
Onset	Early in life "children"	Late in life "adults"
examples	**1-Hemophilia A** (factor VIII deficiency) **2-Hemophilia B** (factor IX deficiency) 3-Hemophilia C (factor XI deficiency) **4-VWD** (von willebrand disease)	1-Severe liver disease(because hepatocytes are the major cell type involved in the synthesis of the coagulation factors). 2-DIC (disseminated intravascular coagulation) 3-acquired hemophilia. 4-anticoagulant drugs (heparin, warfarin) 5-direct oral thrombin inhibitors and direct oral Xa inhibitors. 6-natural anticoagulant mechanisms and the prothrombotic state (thrombophilia). 7-the antiphospholipid syndrome.

❖ First, congenital coagulation disorders:

	1-Hemophilia A	2-Hemophilia B (Christmas disease)
Deficiency in	**Coagulation factor VIII**	**Coagulation factor IX**
incidence	More frequent	Less frequent than Hemophilia A
genetic	**Sex-linked abnormal gene**, *single point mutation* located in **chromosome X** (males are affected and fameless are carriers unless both parents are affected)	
Clinical features	1-If coagulation factors % is **less than 1%** >>severe disease, bleeding even without trauma with **joint deformities and crippling** if not treated, with bleeding into the joints (hemarthrosis) and less frequently into the muscles. **"the knee, elbow and ankles are most commonly affected"** 2-If from **1%-5%** >> moderate disease, bleeding with trauma (post-traumatic bleeding) 3-If from **5%-20%** >> mild disease.	
Detection of carriers and antenatal diagnosis	نقدر نعرف اذا كان الطفل في بطن امه عنده هيموفيليا ولا لا بشيئين: 1-chorionic villus sampling between 11.5 and 14 weeks gestation. (very early) 2-amniocentesis after 16 weeks. Both of them to see fetal DNA	
diagnosis	-Normal PT. -Prolonged APTT. -Normal platelet count and bleeding time.	
	Decreased factor VIII "8"	Decreased factor IX "9"

In the plasma, Factor XIII is only found complexed with VWF, which act as a carrier and prolongs its plasma half-life.

Other deficiencies of factors other than VIII and IX are very rere and they all give rise to bleeding disorders **EXCEPT** factor XII "contact factor"

❖ First, congenital coagulation disorders:

3-The abnormalities in Von Willebrand Disease:

Autosomal dominant with decreased vWF levels (not X-linked)!! The gene for vWF is present on chromosome 12.

The most common inherited coagulation disorder.

What's the function of vWF?

1-it's an adhesive molecule that binds platelets to sub-endothelial tissues.

2-it acts as a carrier for factor VIII. The reduction in vWF results in a reduction in factor VIII concentration.

Symptoms of vWD:

1-spontanous bleeding (usually confined to mucous membranes and skin and takes the form of epistaxes and ecchymoses)

2-bleeding into joints and muscles is RARE.

Von willebrand disease has been divided into 3 types:

1-Type 1 (most frequent): partial reduction of vWF molecules.

2-Type 2: there are qualitative abnormalities.

3-Type 3: nearly complete absence of vWF molecule.(very severe, so you might see bleeding into joints and muscles here)

Type 1 and Type 3 are quantitative. Type 2 is qualitative.

Laboratory findings:

1-increase bleeding time (**NOT** found in hemophilia)

2-increase PTT, normal PT (the same as hemophilia)

3-decreased factor VIII half life. Why? Because vWF normally stabilizes FVIII.

4-abnormal ristocetin test. Why? Ristocetin induces platelet agglutination by causing vWF to bind to platelet GPIb; lack of vWF>> impaired agglutination>> abnormal test.

❖ First, congenital coagulation disorders:

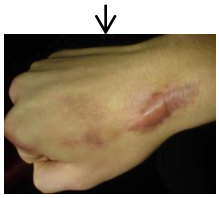
4-Factor XIII (fibrin stabilizing factor) deficiency: (factor 13 is not involved directly with the coagulation cascade)

It's not severe. It can be silent until a bleeding happens.

Factor 13 helps in wound healing,
مثلا لو انسان كان طول عمره ما عنده بليدينق ودخل سوا عملية وبعد العملية شافوا ان الجرح مو قاعد يشفى ولسا يصير منه bleeding هنا على طول فكروا بـFactor XIII

Clinical features of factor XIII deficiency:

1-brusing with minor injury.
2-hematoma after trauma.
3-bleeding (secondary bleeding) (Fibrin clot but dissolve again because there's NO formation of insoluble fibrin).
4-abnormal healing of wound with excessive scar formation (keloid formation).



Laboratory findings:

1-Normal PT and normal APTT.
2-Normal bleeding time and normal platelet aggregation.
3-Normal fibrinogen level.
4-Abnormal clot stability with five molar urea.
5-Low factor XIII level.

❖ Second, acquired coagulation disorders:

1-Disseminated intravascular coagulation (DIC): **Video**

It's a pathologic activation of the coagulation cascad

What is DIC? Is a process in which there is a generalized activation of clotting system followed by marked activation of the fibrinolytic system.
يعني الانسان يصير عنده تخثر بالدم مره كثير لدرجة انه تخلص الcoagulation factorsمن عنده فيبدأ يصير bleeding
It leads to intravascular hemolysis of RBCs.

Laboratory finding:

1-Decrease platelet count.
2-increase PT/PTT.
3-decrease fibrinogen.

❖ Second, acquired coagulation disorders:

Causes of DIC: "almost always secondary to another disease process"			
1-Infections: HIV and hepatitis.	**2-Malignancy:** acute promyelocytic leukemia (M3).	**3-Obsetric complications:** Septic abortion.	**4-Hypersensitivity reaction.**
5-Widespread tissue damage.	**6-Vascular abnormalities:** cardiac bypass surgery, prosthetic valves.	**7-Miscellanous:** Liver failure, snake and invertebrate venoms.	

-Elevated fibrin degradation product (FDPs), particularly D-dimer.
-Elevated D-dimer is the best screening test for DIC.

2-acquired hemophilia:

-It's due to autoantibody-mediated factor VIII deficiency.
-Occur in either sex (males AND females).
-More common in **elderly**.
-High mortality.

➢ Check your Understanding! (HERE)

= Haematology 435 =

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Or on twitter