Lec (2)
Inherited coagulation disorders

Objectives

To Know the classification Etiology, Pathology and to learn the diagnosis of Inherited coagulation factors disorders

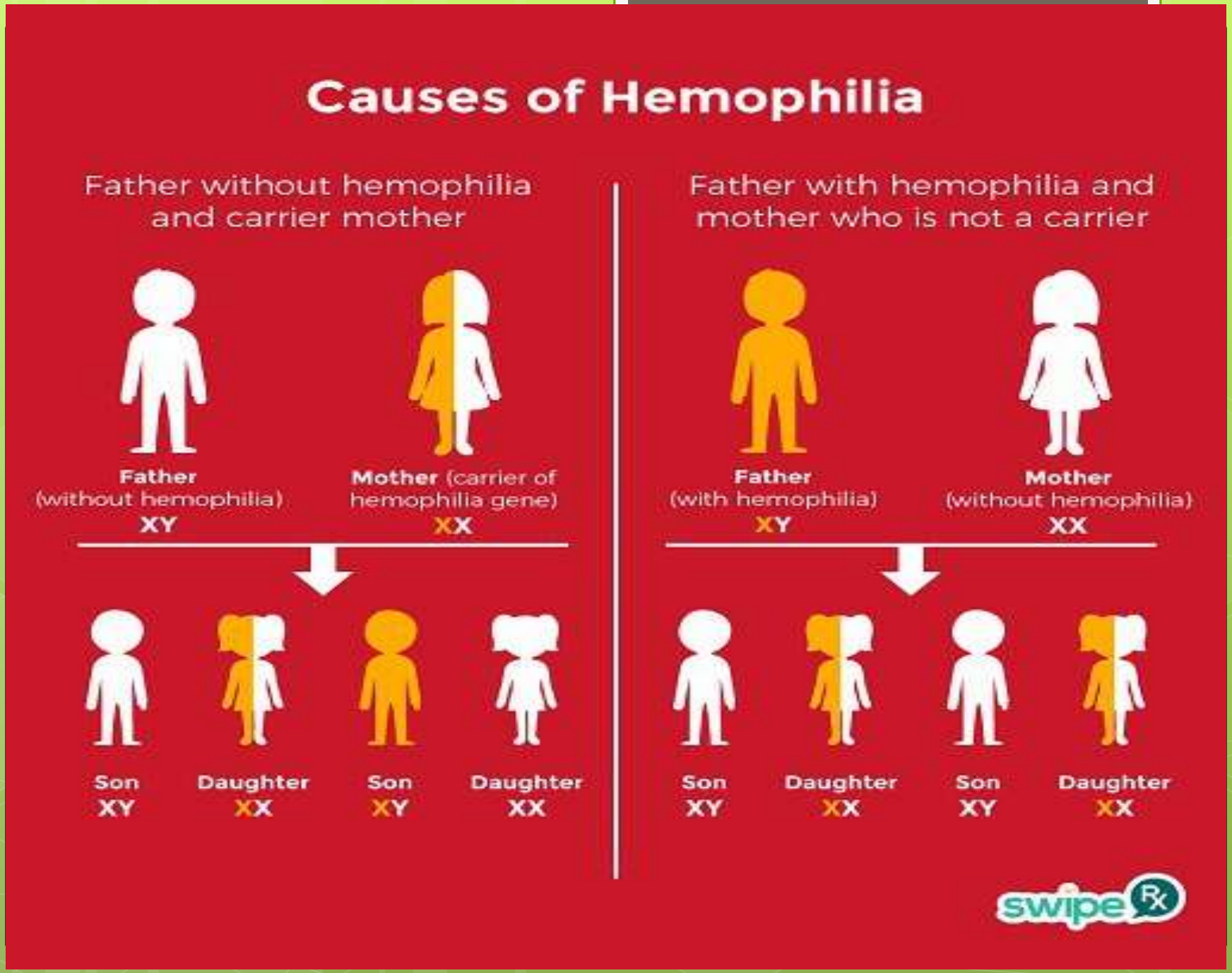
Hemophilia A

Factor VIII

- Gene located on long arm of chromosome X.
- Plasma level 50-150% (50-150 u/dl)
- Plasma half life 10-12 hrs
- Function as cofactor in tenase complex
- Synthesis site; mainly from liver, and may be from lung, spleen and endothelia cells.

Prevalence and Genetic basis

- Most common hereditary clotting factor deficiencies.
- Incidence is (1:10 000) male birth.
- Life expectancy is now approaching normal.
- A sex linked inherited disorder due to deficiency of factor VIII.
- Positive family history in 70% of cases and in 30% is due to new mutation.
- The defect is absence or reduce level of factor VIII.
- Carrier of hemophilia A are females with average 50% of plasma factor level, and 50% of carriers have low factor level. Variable levels in female according to random inactivation of X chromosome (lyonization).


Causes of Hemophilia
Father without hemophilia and carrier mother
Father (without hemophilia) XY
Mother (carrier of hemophilia gene) XX
Son XY
Daughter XX
Son XY
Daughter XX
Father with hemophilia and mother who is not a carrier
Father (with hemophilia) XY
Mother (without hemophilia) XX
Son XY
Daughter XX
Son XY
Daughter XX
swipe Rx

Clinical features

- Males are affected. Female can be affected, but usually carrier.

- Features start usually when the infant starts to crawl, or even during labor or circumcision.

- One of the main features is Hemoarthrosis into the bearing joints with subsequent target joint formation.
- Other common feature is bleeding into the muscles.

- Painless spontaneous hematuria, gastrointestinal bleeding, CNS bleeding, post operative hemorrhage, post dental extraction hemorrhage.

- The most impressive feature in hemophilia is not the rate of hemorrhage but its persistency. The clot is bulk, friable, and break off with rebleeding over days or weeks.

(Normal Factor VIII level in plasma is 50-150 U/dl), clinical significant occur when factor level < 30 U/dl.

Correlation of coagulation factor level and severity of disease:

- Mild Hemophilia A ---------- Level 6-30 U/dl.

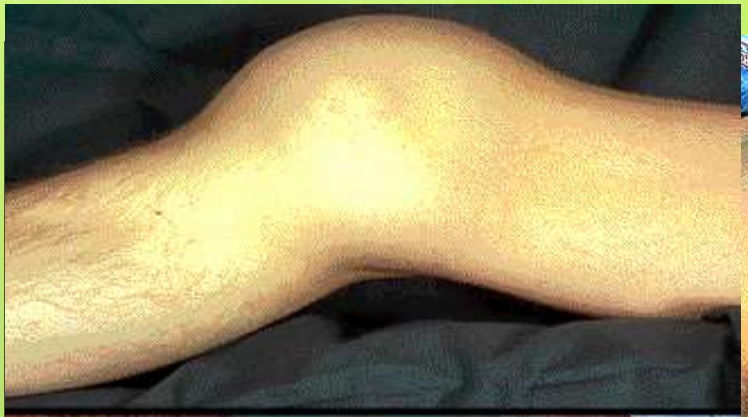
(post traumatic hemorrhage)

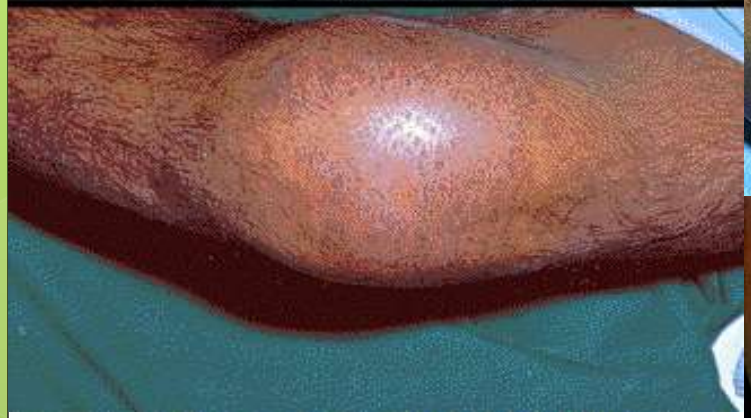
- Moderate Hemophilia A ---------- Level 1-5 U/dl

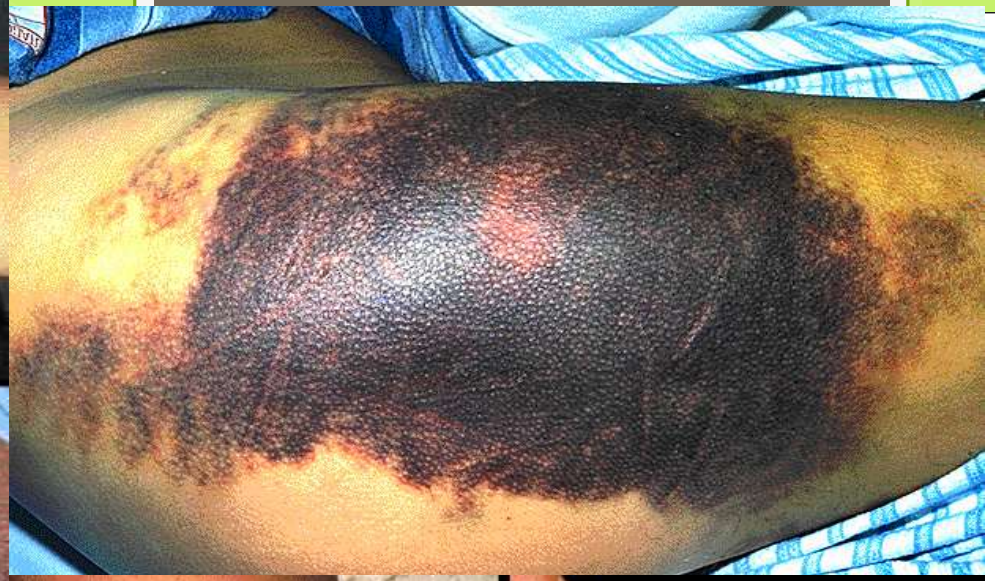
(post traumatic and occasional spontaneous)

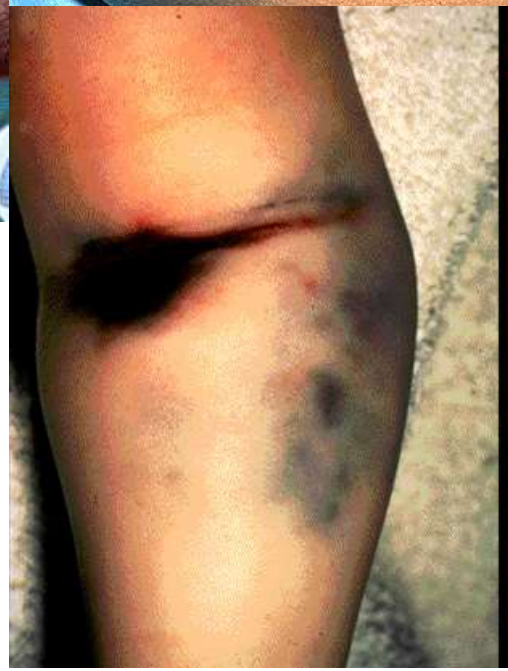
- Sever Hemophilia A ---------- Level <1 U/dl.

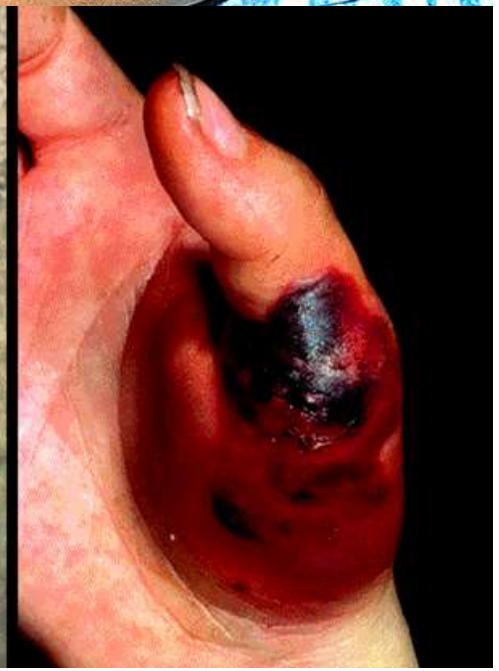
(frequent spontaneous hemmorrhage and joint deformity)

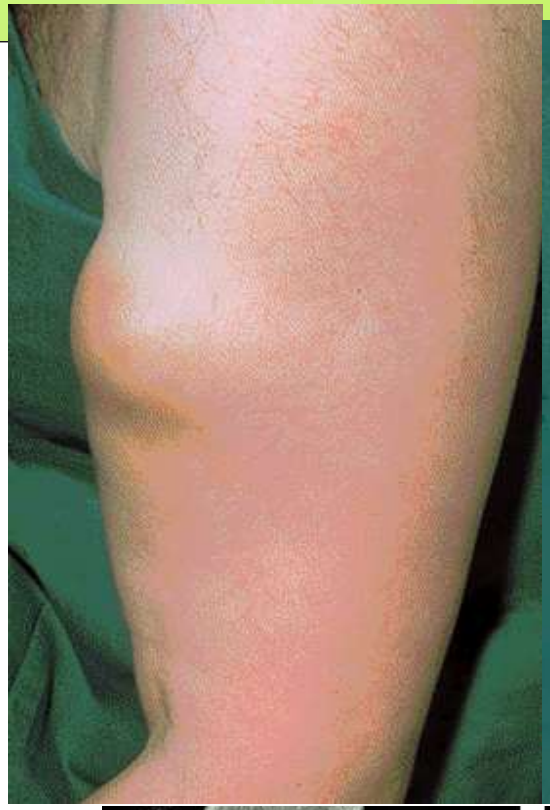


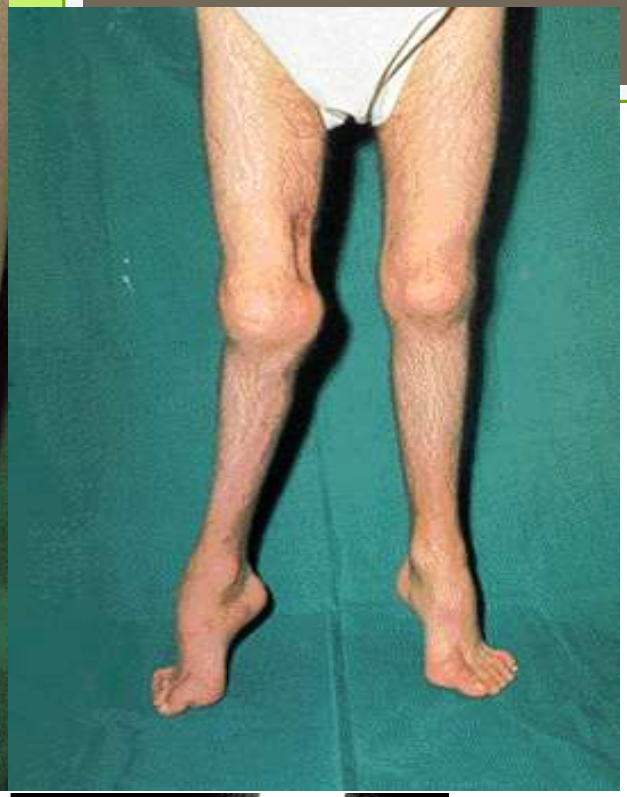


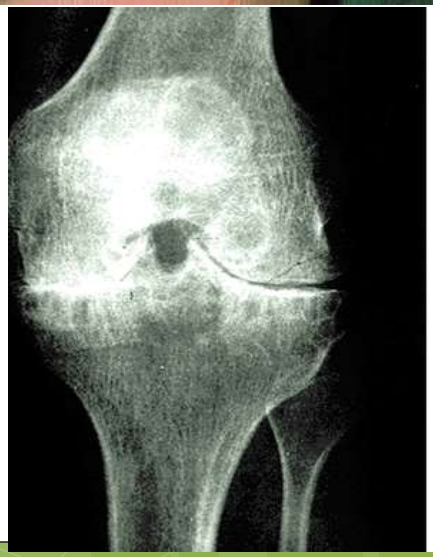


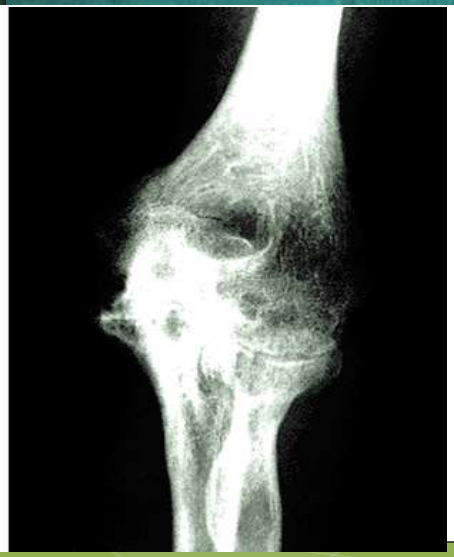












Laboratory findings

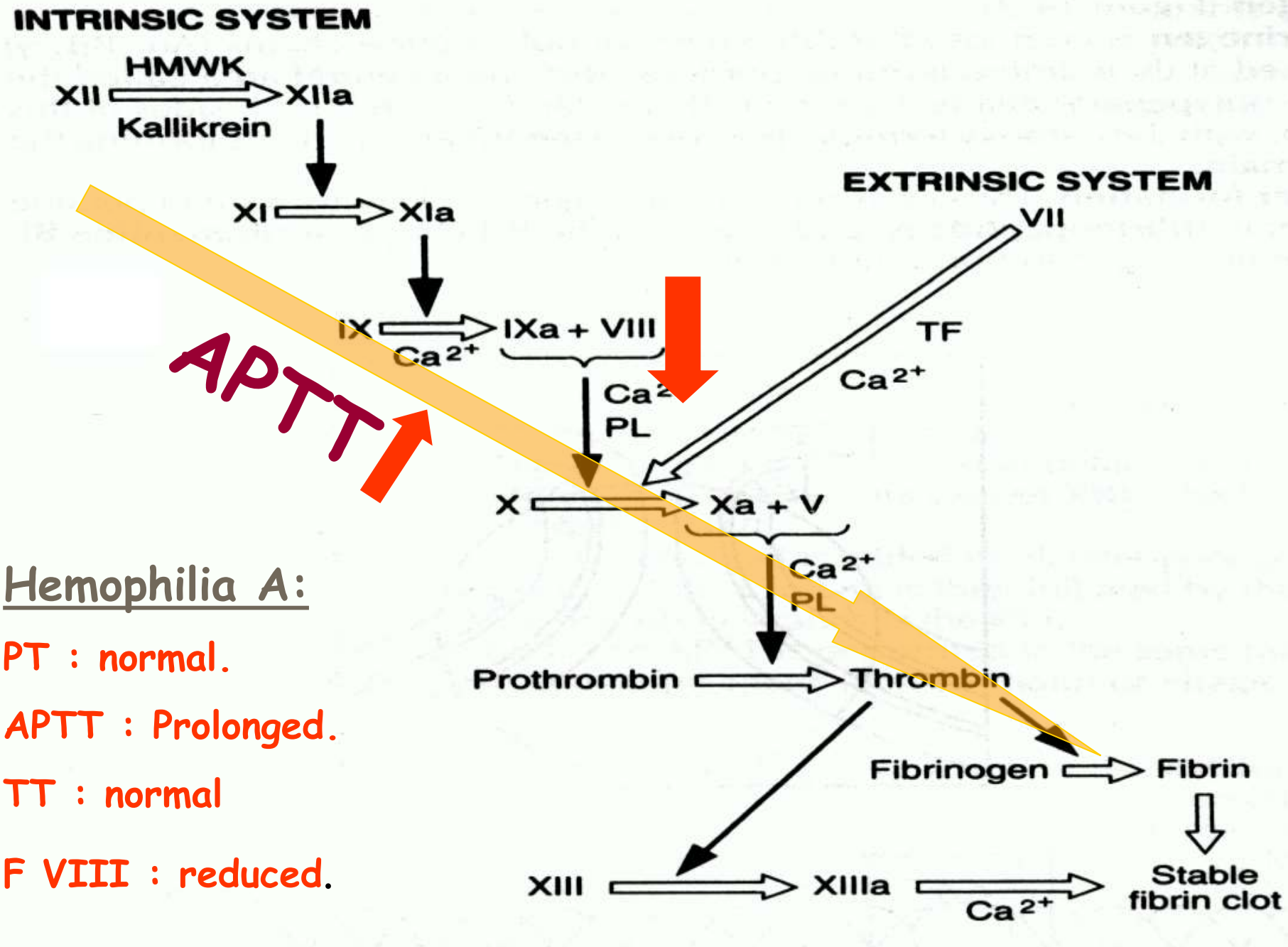
All screenings test (platelets count, bleeding time, PT, TT) are normal except prolonged APTT.

Corrected APTT with normal plasma, but not corrected with factor VIII deficient plasma.

* Plasma (Patient)+ Plasma (Normal person) = Normal APTT
* Plasma (Patient)+ Plasma deficient in VIII= Prolonged PTT

Factor VIII assay showing reduced Factor VIII concentration.

Antenatal diagnosis using DNA techniques to chorionic villous biopsy at 8-10 wk or detection of factor level using fetal blood sampling at 16-20 wk .



Hemophilia A:

PT : normal.

APTT : Prolonged.

TT : normal

F VIII : reduced.

Hemophilia B
(Christmas disease)

- Inheritance and C/F same to hemophilia A
- Principle of replacement therapy similar to Hemophilia A, and bleeding treated with F9 concentrate but the dose given single daily due to its longer half life
- Lab findings are prolonged APTT, corrected with normal plasma, but not corrected with factor IX deficient plasma.

* Plasma (Patient)+ Plasma (Normal person) = Normal APTT
* Plasma (Patient)+ Plasma deficient in VIII= Normal APTT
* Plasma (Patient)+ Plasma deficient in IX = Prolonged APTT

VonWillebrand's Disease

VWF (Von Willebrand's Factor)

- Gene located on chromosome 12.
- Functions are carrier protein of Factor VIII (carrier and protection) and Platelets adhesion to subendothelium.
- Plasma level 50-150%
- Variable half life.
- Synthesis site; vascular ECs and Megakaryocytes.
- There are small, intermediate and large MW multimers of VWF with special flanking bands.
- Ultra large VWF multimer after secretion is rapidly cleaved by metalloproteinase (ADAMTS-13).

Relation between vonWillebrand's Factor (vWF) and Factor VIII

Prevalence and Genetic basis

- Most common hereditary bleeding disorders.

- Prevalence is 0.8 %.

- The defect is absence, reduction or dysfunction in VWF due to point mutation or major deletion.

- Majority is Autosomal dominant and rarely Autosomal recessive disease.

Clinical features:

- Mucous membrane bleeding, particularly epistaxis and menorrhagia.
- Bruising and bleeding after trauma or during surgery are also common.
- Haemarthrosis and muscle hematoma are rare except in type 3.

Classification of VWD:

Type I (75%) Quantitative / Mild deficiency in VWF.

Type III (rare) Quantitative / Absent in VWF.

Type II (15-20%) Qualitative / Dysfunction in VWF.

- 2A: absent of high and intermediate multimers
- 2B: increase affinity of GPIb for platelets (mutation in GPIb)
- 2M: loss of platelets binding activity (mutation in GPIb)
- 2N: decrease in F8 binding capacity

Diagnosis of VWD:

- Prolonged Activated Partial thromboplastin time (APTT).
- Bleeding time classically prolonged.
- Platelets count normal except in type 2B with low count.
- VWF Ag is reduced.
- Specific tests for type 2, platelets-dependent VWF activity and factor VIII coagulant activity

Thanks