This lecture was done by 432 Physiology Team

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Haemostasis in Health and Disease

432 ***Hematology*** *Team*

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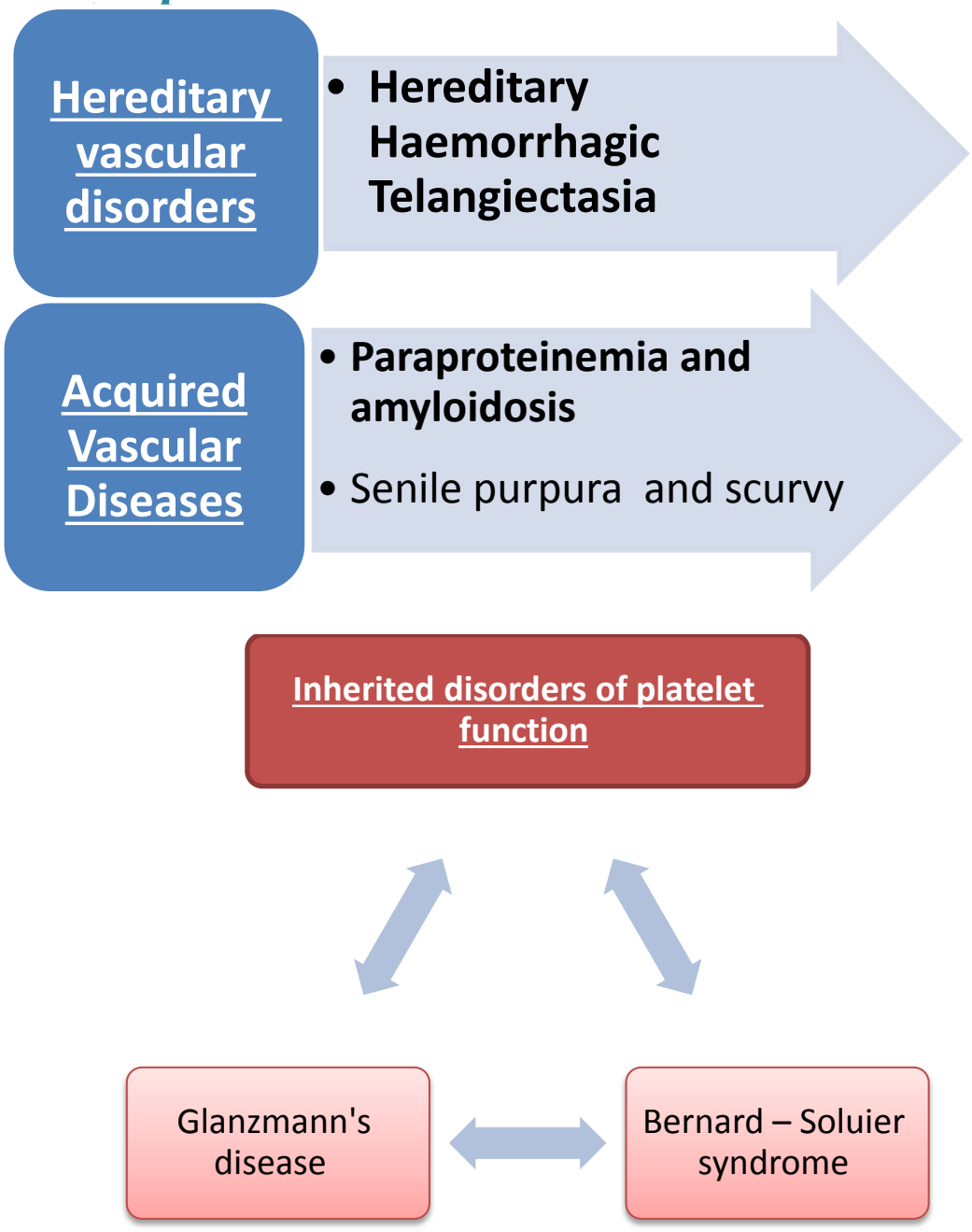
Color Index: Female notes are in Green. Male notes are in Blue. Red is important. Orange is explanation.

Haemostasis in Health and Disease

Mind Map:



Hemostasis

Introduction

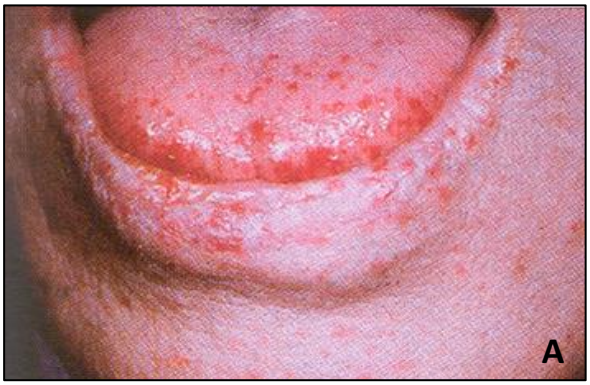
The most important feature of platelet disorders is presenting with bleeding "the dangerous one" or thrombosis.

Normally, there are 3 important factors to prevent bleeding:

1- Normal blood vessels.
2- Normal platelet count "150-400x10^9/L" and they are also functioning normally.
3- Presence of clotting factors.

1- Hereditary vascular disorders:

- **Hereditary Hemorrhagic Telangiectasia** "the common one worldwide" (Rendu-weber-osler syndrome).
  More common in old age abnormal blood vessel formation in the skin, mucous membranes (pic A)
- Kasabach-merritt syndrome (Haemangioma – Thrombocytopenia).
- Ehlers-Danlos syndrome.
- Pseudoxanthoma elasticum.
- Homocystinuria.
- Marfan syndrome.
- Osteogenesis imperfect.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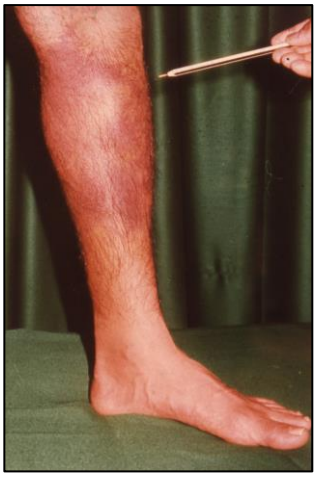
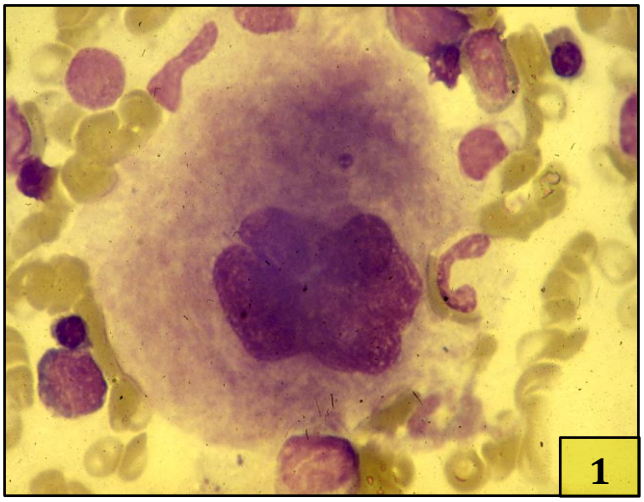
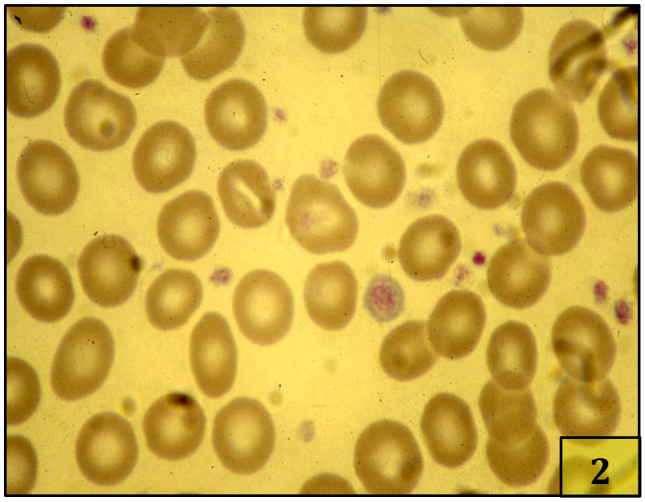
2- Acquired Vascular Diseases:

- Allergic purpura (Henoch-Schonlein purpura).
- **Paraproteinemia and amyloidosis** here there is abnormal protein participates on the blood vessels.
- Senile purpura due to changes happen with increasing in age as the skin and the vessels become more fragile and is seen more commonly in old males as a dark purble discoloration especially in the hands and upper limps.
- Drug-induced vascular purpuras (Steroid therapy, sulfonamides, iodides, aspirin, digoxin, methyldopa, estrogen, allopurinol, penicillin and other antibiotics).
- Vitamin C Deficiency (Scurvy).
- Purpura simplex (Easy brusability).
- Psychogenic purpura.
- Purpura associated with infections as in DIC.



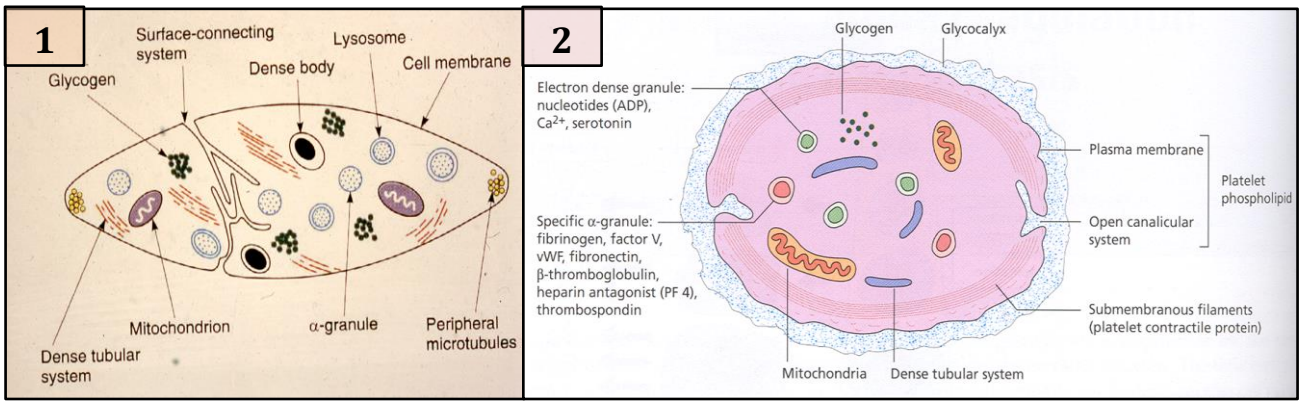
Normal platelets Count =	**150-400x10^9/L**
Normal Platelet Size (MPV) =	**7.3-11.1 Fl**
NORMAL PLATELET DIAMETER =	1-2.5 µ
Normal Platelet Life Span =	**7-10 DAYS**
Platelet Formation is by segmentation of the cytoplasm of the Megakaryocyte "The Mother of Platelets" **in the bone marrow.**	





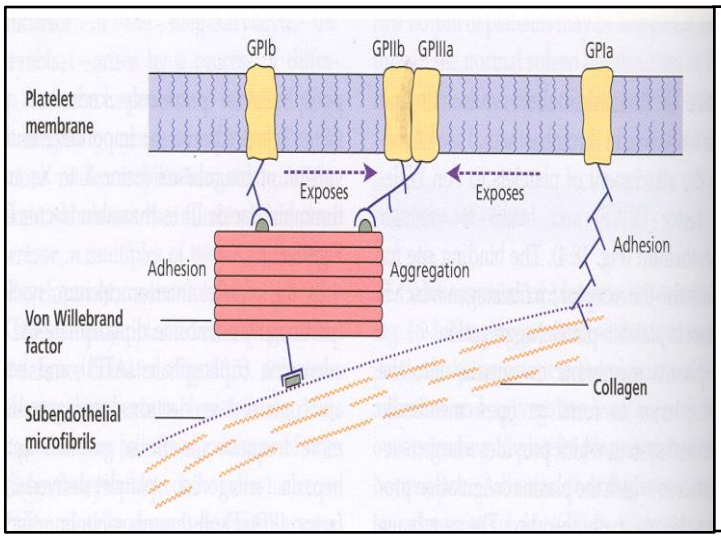
[1] Megakaryocyte in the bone marrow has abundent purble cytoplasm which later fragmentate and gives the platelets **(one megakaryocyte gives 1000 platelets).**
[2] Platelets appear in the peripheral blood film as small purble dots.

Structure of Platelet:



[1] It has storage granules include: Dense body – lysosomes – α-granule.
[2] Contents of these granules.

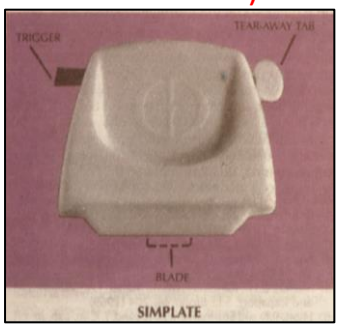
Normal platelet membrane has these glycoproteins (Gp1b – Gpllb/llla – Gp1a) which is important in platelet adhesion along with vW factor

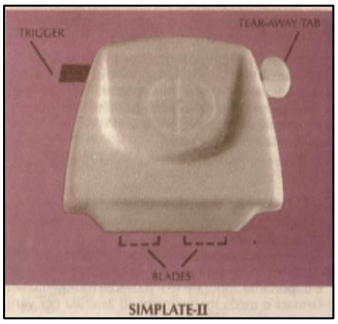


- When there is a vessel injury Gp1a will cause directly adhering of platelets with collagen in the subendothelial microfibrils while the other glycoproteins stimulate more platelets via binding with vW factor (aggregation).
- vW factor comes from subenothelial tissues and megakaryocytes and its deficiency is more associated with congenital anomalies.
- **Gp1b** deficiency is associated with **Bernard-Soluier syndrome**.
- **GpIIb/IIIa** deficiency is associated with **Glanzmann's disease**.

Measurement of Platelet Function by:

1) Bleeding time test results is normally range **from 3-8 min.**
(this test also measures vWF)





2) Platelet aggregation test: is specific for platelets and performed by adding some substances (e.g. collagen, ADP, Arachidonate, Ristocetin) to the platelets and the result of the reaction comes on graph.

DEFECTIVE PLATELET FUNCTION

A defect in function is suspected if there is **prolonged bleeding time with or without skin or mucosal hemorrhage** in the presence of **normal platelet count**. "From 430 team work"

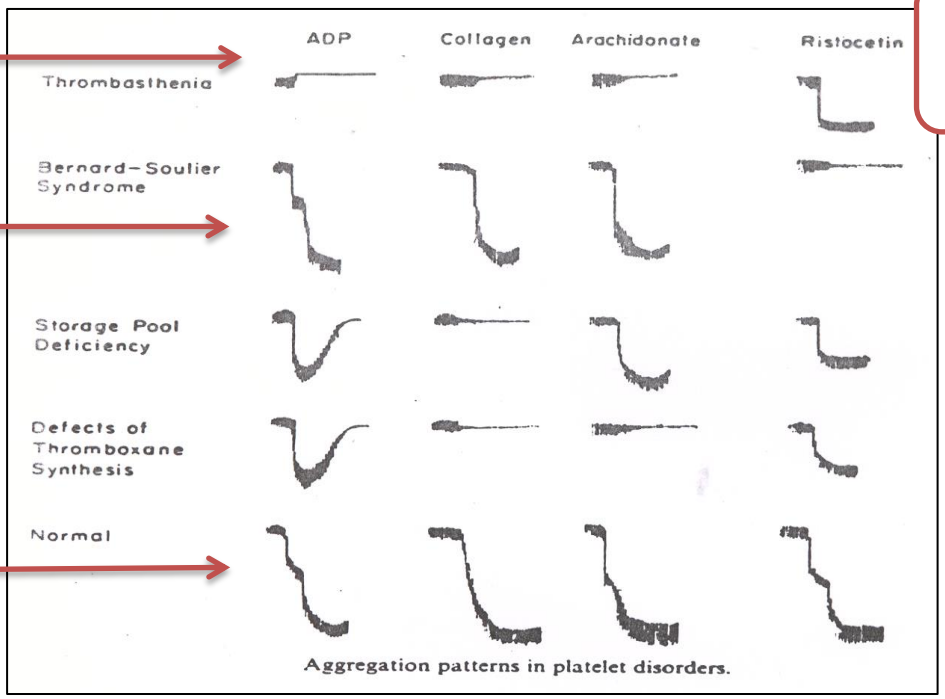
A\ Inherited disorders of platelet function:

- **Membrane abnormalities:**
  - Bernard – Soluier syndrome which is common worldwide.
  - Thrombasthenia also known as Glanzmann's disease and is more common in our region.
  - Platelet factor – 3 deficiency
- **Intracellular abnormalities: 1+2+3**
  1- **Storage-pool (dense body) deficiency:**
  Hermansky – Pudlak syndrome
  Wiskott – Aldrich syndrome
  Chediak – Higashi syndrome
  Thrombocytopenia with absent radii
  Idiopathic storage – pool disease

2- **α- granule deficiency:**
   Gray platelet syndrome (in blood film, the platelets appear gray in color).
3- **Combined deficiency of dense bodies and α-granules:**
   - Defects of thromboxane synthesis: problem in the enzymes
     - Cyclo-oxygenase deficiency
     - Thromboxane synthetase Deficiency
     - Defective response to thromboxane
   - Miscellaneous:
     - Epstein's syndrome
     - May-Hegglin anomaly

In **Thrombasthenia** there is no reaction (linear) except with **Ristocetin**, while in **Bernard- soulier syndrome**, the platelets will react normally except with (Ristocetin)

Normal platelet will react with the 4 substances



Aggregation patterns in platelet disorders.

Important especially the first 2 patterns

B\Causes of Acquired Platelet Dysfunction:

Uraemia - Myeloproliferative disorders - Multiple Myeloma – Drugs e.g. Aspirin – Scurvy – Sever Burns – Valvular and congenital heart disease.

Thrombocytopenia "decreased platelets count":

Causes include:

1\ Failure of platelet production a+b

a- Selective megakaryocyte depression e.g.:
   Rare congenital defects, drugs, chemicals, viral infections.

b- Part of general bone marrow failure
   Cytotoxic drugs, Radiotherapy, Aplastic Anaemia, Leukaemia, Myelodysplastic syndromes, Myelofibrosis, Marrow infiltration (e.g. Carcinoma, Lymphoma and Multiple myeloma), Megaloblastic anaemia, HIV infection.

2\ Increased Consumption of Platelets in the peripheral circulation:

a) Immune causes:
   - Autoimmune (idiopathic).
   - Associated with: systemic lupus erythematosus, chronic lymphocytic leukemia or Lymphoma.
   - Infections: HIV, other viruses, malaria.
   - Drug-induced (e.g. Heparin).
   - Post-transfusional purpura.
   - Feto-maternal alloimmune thrombocytopenia.

b) Disseminated intravascular coagulation which is characteristic for M3 leukemia.

c) Thrombotic thrombocytopenic purpura.

d) Abnormal distribution of platelets (e.g. Splenomegaly)
   Normally 30% of platelets are trapped but in splenomegaly it will increase up to 70%

e) Dilutional loss (e.g. massive transfusion of stored blood to bleeding patients).

Clinical features of immune thrombocytopenia (ITB):

- It develops more commonly in children after infection
- **ITB is associated with mucous membrane bleeding**

Degree of Thrombocytopenia	Symptoms	Physical findings
Mild (>50 000/mm^3)	None	None
Moderate (30-50 000/mm^3)	Bruising with minor trauma	Scattered ecchymoses at trauma site
Severe (10-30 000/mm^3)	Spontaneous bruising. menorrhagia	Petechiae and purpura, more prominent on extremities
Marked (<10 000mm^3)	spontaneous brusing, mucosal bleeding, risk for CNS bleeding	Generalized purpura, epistaxis, GU bleeding CNS symptoms

Laboratory features of immune thrombocytopenia:

- Thrombocytopenia with increased numbers of large platelets (>2.5µ)
  The megakaryocytes lose control and produce platelets of different sizes
- In bone marrow examination, increased numbers and size of megakaryocytes.
- Reduced intravascular platelet survival due to increased turnover.
- Elevated levels of platelet-associated IgG which confirm the diagnosis.

Thrombotic thrombocytopenic purpura (TTP)- Hemolytic-uremic syndrome (HUS):

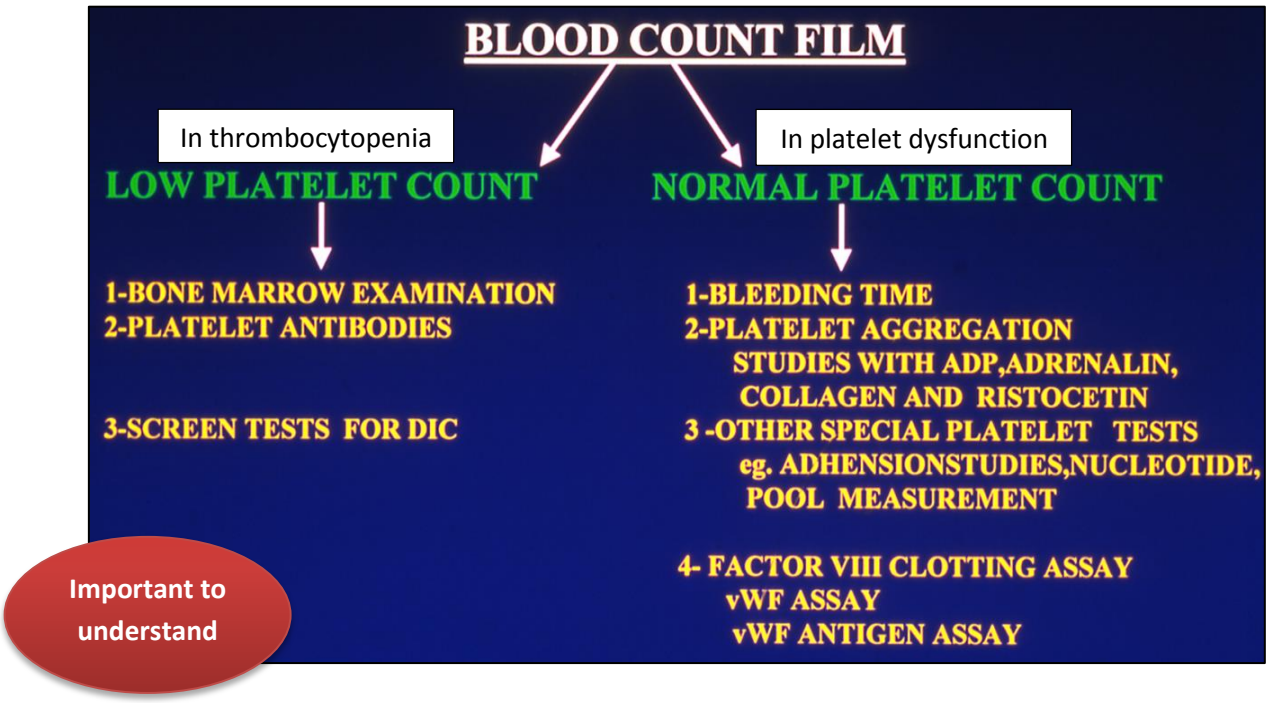
Clinical Features:

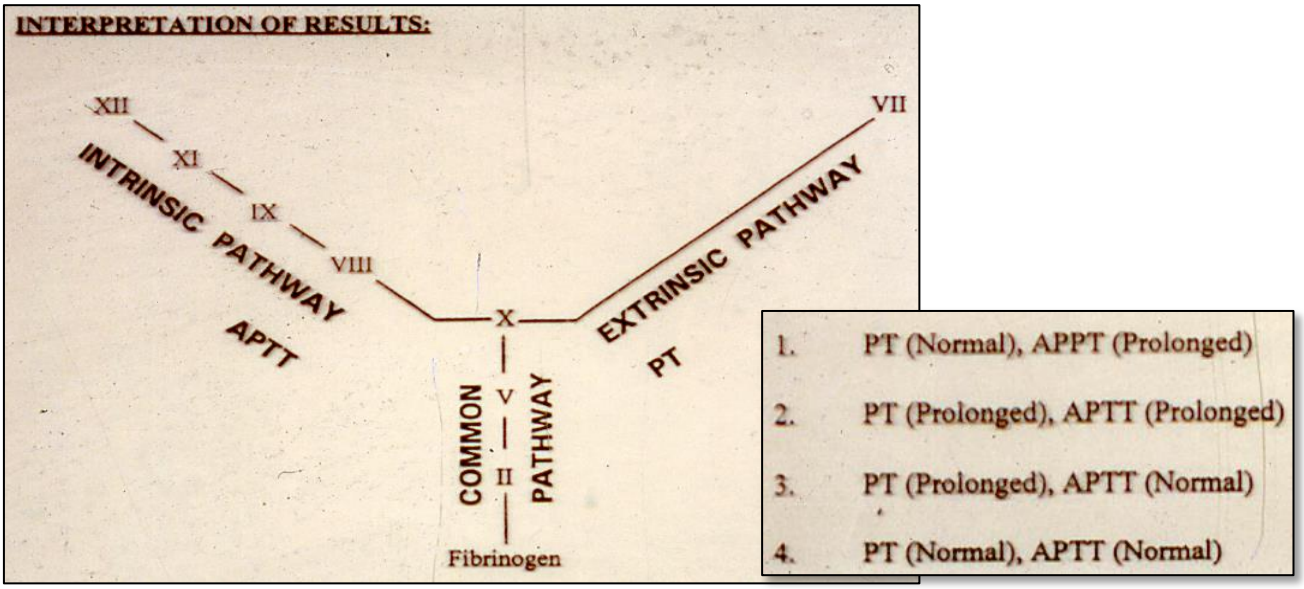
- **Fever.**
- **Thrombocytopenic purpura.**
- **Hemolytic anemia.**
- **Neurological symptoms.**
- **Renal dysfunction.**

(It associates with other condition and also with genetic predisposition).

Causes:

- **Infections (E.coli type 0157, Shigella dysenteriae serotype 1, and viral infection).**
- Hypersensitivity.
- Oral contraceptive.
- Autoimmune diseases e.g. SLE and rheumatoid arthritis.
- Chemotherapy.





When patient comes for the first time and needs an immediate operation, doctor must do CBC and Coagulation profile which indicate:

- Prothrombin time (10-14s) → covers the extrinsic pathway, mainly factor VII.
- Activated Partial Thromboplastin Time (30-40s) → covers the intrinsic pathway, measure factors XII, XI, IX and VIII.
- Thrombin time → measures Fibrinogen.

HEMOPHILIA

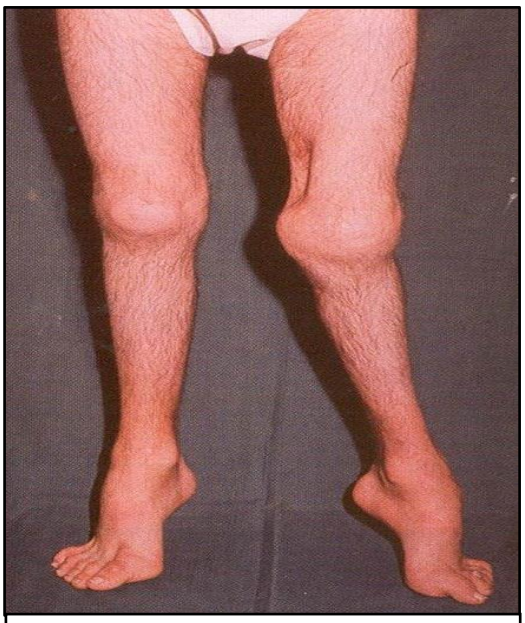
There are 3 types of hemophilia:

1. Hemophilia A in factor VIII deficiency.
2. Hemophilia B in factor IX deficiency.
3. Hemophilia C in factor XI deficiency *"newly discovered"*

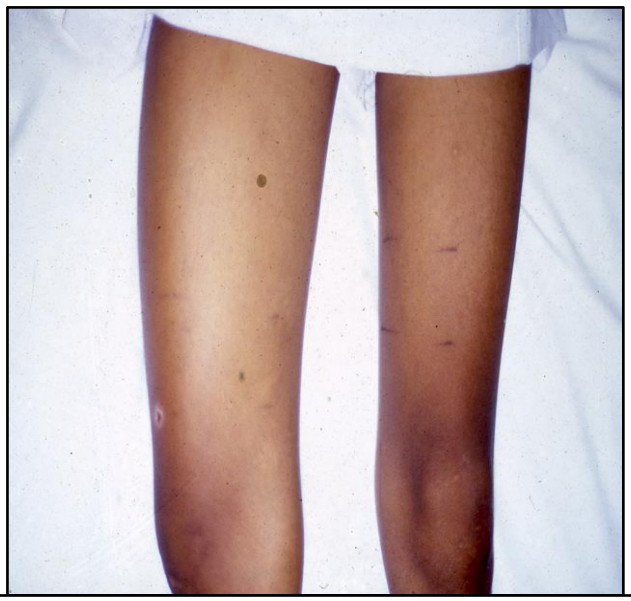
Correlation of coagulation factor activity and disease severity in hemophilia A or hemophilia B

Coagulation factor activity (percentage of normal)	Clinical manifestations
<1	Severe disease Frequent spontaneous bleeding episodes from early life Joint deformity and crippling if not adequately teated
1 – 5	Moderate disease Post-traumatic bleeding occasional spontaneous episodes
5 – 20	Mild diesease Post-traumatic bleeding

Some features of clinical manifestation in sever conditions:



Joint deformity



Interreticular bleeding "hemoarthrosis" and Intramuscular bleeding

Diagnosis of Haemophilia A & Von – Willebrand's

Haemophilia A	VW Disease
Bleeding time normal	Bleeding time abnormal ★
PT normal	PT normal
PTT abnormal	PTT abnormal
Factor VIII C ↓	Factor VIII C ↓
VWf : normal	vWf ↓
Factor VIII related antigen vMF antigen: normal	vMF antigen ↓
Ristocetin co-factor normal	Ristocetin co-factor low
Platelets aggregation normal	Platelets aggregation abnormal ★

Classification of vW disease:

Type 1: Partial quantitative deficiency
Type 2: Qualitative deficiency (functional abnormality)
Type 3: Complete quantitative deficiency

Treatment of Haemophilia

1. Factor VIII replacement therapy
   a. Immunoaffinity –purified Factor VIII preparation
   Dose of Factor VIII to be infused (units) = weight (kg) x increment needed (u/dL)/2
   b. Reconbinant Factor VIII (five different commercial preapartions)

2. DDAVP (desmopressin) I.V or S.C or nasal spray

3. Local supportive measures

4. Prophylactic treatment
   - Factor VIII three time / week
   - Vascular access device such as Port-a-Catch if venous access is difficult

5. Social and psychological care

6. Multidisciplinary team management
   - Haematologist, Dental, Orthopaedic , Physiotherapist

7. Gene therapy.

Treatment of Von Willebrand Disease

a. Local measures

b. Antifibrinolytic agent (tranexamic acid for mild bleeding)

c. DDAVP infusion for type I VWD

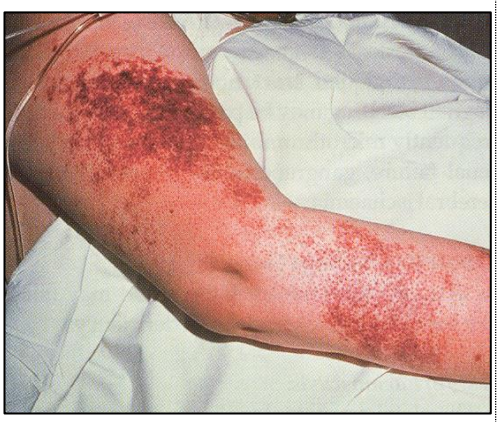
d. High purity factor VWF concentrates for patient with very low VWF levels
   - Factor VIII concentrate may also be given for more rapid correction.

e. Social and psychological care.

Disseminated intravascular coagulation (DIC)

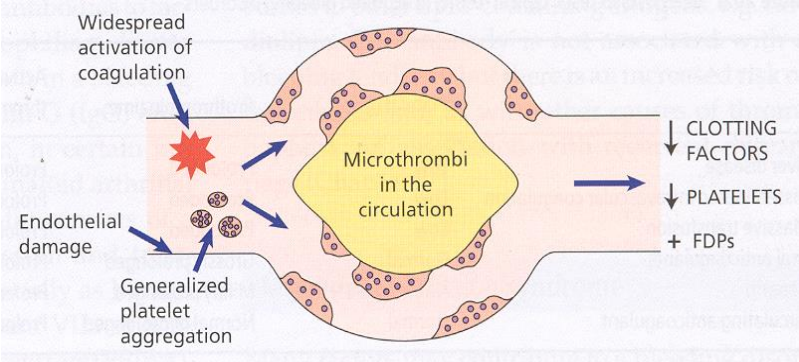
'CONSUMPTION COAGULATIONPATHY' DEFIBRINATION SYNDROME

- There is Abnormal increased of fibrin in the circulation



Important causes include:

- **Infections:**
  - Gram-negative and meningococcal septicemia.
  - Clostridium welchii septicemia.
  - Severe Falciparum malaria.
  - Viral infection – varicella, HIV, hepatitis, cytomegalovirus.
- **Malignancy:**
  - Widespread mucin-secreting adenocarcinoma.
  - Acute promyelocytic leukemia. (AML-M3)



Laboratory findings:
- Decreased clotting factor due to increased consumption.
- Decreased platelet count.
- Presence of fibrin degradation products.

Screening Tests of Hemostasis:

Screening tests	Defects
B.T. Prolonged	Platelets (↓ or dysfunction) + Von Willebrand's disease
APTT prolonged	Factors: XII, XI, VIII, IX, X, V, II, I
P.T. Prolonged	Factors: VII, X, V, II, I
T.T. Prolonged	Fibrinogen (Factor I) high FDPS
Reptilase time prolonged	Fibrinogen (factor I) high FDPS. Not effected by Heparin therapy
FDPS high	▪ D.I.C. ▪ Snake Bite ▪ Thrombolytic therapy ▪ Dysfibrinogenemia
Platelet Count Low	Thrombocytopenia
Platelet Count Normal	Platelet dysfunction

Summary

- The most important cause of hereditary disorders is Hemorrhagic Telangiectasia.
- Platelet Formation Is By Segmentation Of The Cytoplasm Of The Megakaryocyte in the bone marrow.
- Normal platelet membrane has these glycoproteins (GP1b – Gpllb/llla – Gp1a) which is important in platelet adhesion along with vW factor.
- There are 3 types of hemophilia:
  Hemophilia A in factor VIII deficiency.
  Hemophilia B in factor IX deficiency.
  Hemophilia C in factor XI deficiency.
- DIC…. there is Abnormal increased of fibrin in the circulation.
- Causes of DIC:
  1- Infection
  2- Malignancy

Questions

1/ what is the most important cause of hereditary vascular disease?

A) Haemorrhagic Telangiectasia
B) Marfam syndrome
C) Homocystinuria

2/ Increased consumption of Platelets can cause which of the following?

A) Thrombocytosis
B) Leukocytosis
C) Thrombocytopenia

3/ Hemophilia A is due to deficiency of which of the following factors?

A) VI
B) XII
C) VIII

Answers:

- 1- A
- 2- C
- 3- C

اللهم إني استودعك ما قرأت و ما حفظت و ما تعلمت فرده عليَ عند حاجتي إليه انك على كل شيء قدير

If there is any mistake or feedback please contact us on: 432PathologyTeam@gmail.com

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Good Luck! ^_^