Hematology

Problem Based Learning

☑ Sheet ☐ Slide ☐ Handout

Number: 3

Subject: Bleeding Disorders

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Price:

بسم الله الرحمن الرحيم

- This sheet was written according to section 2 recording.
- Things written in *Italic* were not mentioned in the lecture

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☆ Causes of abnormal bleeding (bleeding tendencies)

1. Abnormal Blood vessels **(Vascular disorders)**
2. Abnormal Platelets (**Quantitative** or **Qualitative**)
3. Defective or Deficient **Coagulation factors**.(could be inherited or acquired)
4. Excessive **Fibrinolytic system** (Anticoagulation factors)

- All will lead to an increase in bleeding time.

➢ Vascular disorders:

- Causes bleeding in the **skin** and **mucous membrane**

Acquired vascular defects:
(they cause defects in collagen fibers of vessel wall mainly)

1. **Senile Purpura**: due to atrophy of perivascular connective tissue**.**
2. **Scurvy:** Vit C deficiency
3. **Steroid purpura (defective CT).**
4. **Hereditary hemorrhagic telangiectasia:** abnormal formation of vessels with variable thickness of the wall, which makes them weak and causes bleeding
5. **Ehlers-Danlos syndrome:** congenital disease, causes defects in collagen
6. **Vasculitis:** collagen vascular diseases that causes weakness in the vessel wall –> bleeding

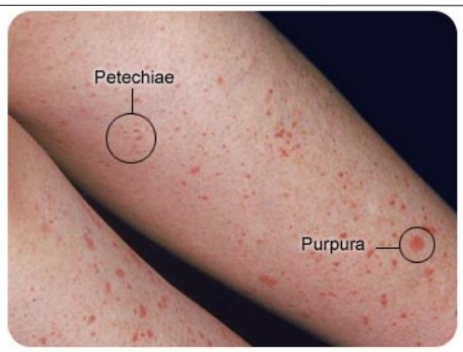
   -Hypersensitivity:

   Henoch-Schoenlein purpura

   - Septic Vasculitis: infections.

   Measles, dengue fever, meningococcemia, ricketsial infections, bacterial endocarditis

Note that : Petechiae is a small bleeding in the skin 1-3mm in diameter while Purpura is larger than petechiae with diameter of 3-10mm



Petechiae	1-3mm
Purpura	3mm-10 mm
Ecchymosis	>10mm

➢ Platelets Defects:

1. Quantitative (Thrombocytopenia)
2. Qualitative (Platelet Function Disorder)

- **Quantitative**: normal platelet count is 150,000-450,000 per µL,
  - Between 50,000-100,000 bleeding may occur after severe trauma or surgery, about 70,000 is enough however the problem is when its below 5,000 count fatal spontaneous bleeding may occur in the brain, eyes or lungs, so prophylactic platelet transfusion is advised even in patients with platelet count between 10,000-20,000 and below
  - For medical procedures it's preferred to keep the platelet count above 50,000, but for major surgery, brain surgery or eye surgery it should be above 100,000

Classification of Thrombocytopenia:

- **Failure of production:**
- **Increased platelet destruction**
- **Sequestration: hypersplenism**
- **Dilutional**

❖ **Failure of production**: either increased or decreased megakaryocytes,

- **Decreased BM megakaryocytes**
  - Infiltrative diseases of BM
  - tumors originated in (leukemia, lymphoma) or metastasized to (carcinoma) the BM
  - Aplastic BM "aplastic anemia"
  - fibrosis
  - *Amegakaryocytic thrombocytopenia*
  - *HIV infection*
  - *Drugs*

Increased BM megakaryocytes

"ineffective megakaryopoiesis"

- Megaloblastic anemia
- Myelodysplasia
- Alcohol induced
- Rare diseases such as Wiskott-Aldrich syndrome

If we did a **BM** exam and we saw megakaryocytes and platelet count was low, its most likely decrease in production however sometimes we see these megakaryocytes but there are ineffective

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❖ Increased Destruction:

Due to :

1. Destruction mainly occurs in the **Spleen**
2. **Auto-immune** destruction, by anti-platelet antibodies, causes immune thrombocytopenia, primary is **ITP** "Idiopathic Thrombocytopenic purpura", secondary acquired diseases like **SLE** "systemic lupus erythematosus", HIV Or CLL.
3. Drug related thrombocytopenia: **quinidine and heparin (note that:** Most common cause is administration of **Heparin**, which causes HIT "heparin-induced thrombocytopenia")
4. **Post transfusion** thrombocytopenia: after receiving blood patients produce **Alloantibodies** that attack their own platelets
5. **Neonatal** thrombocytopenia: same as post transfusion, **Alloantibodies** or **Autoantibodies** come from the mother through the placenta and attack the fetus platelets

Idiopathic Thrombocytopenic Purpura "ITP"(primary autoimmune)

- **High incidence in women of child bearing age.**
- **Autoantibodies against GP IIb/IIIa, or Ib/IX.**
- **Platelets lifespan reduced to hours.(normally it's days)**
- **Megakaryocytes increased.**
- **Petechial bleeding, easy bruising, menorrhagia.**

➢ **Diagnosis:**

- **Decreased platelet count (10-50x10^9/l).**
- **Hb. and WBCs are normal.**
- **Increased megakaryocytes numbers in BM.**
- **Antiplatelet antibodies, Antinuclear antibodies in SLE.**
- **Coomb's test in Evan's syndrome.**

➢ **Treatment:**

- **Steroids (to decrease antibodies), so as Immunosuppressive therapy.**
- **Splenectomy.**
- **High dose IV immunoglobulins against those Anti-platelets Abs**

Note: Platelets transfusion is Not helpful since the body will still attack them

There is **Acute** ITP which Affects **children,**

- ***Preceded by infection or vaccination in 75% of cases.***
- ***Spontaneous remission in >90% of cases.***
- ***Severe cases benefit from steroids or IV immunoglobulins***

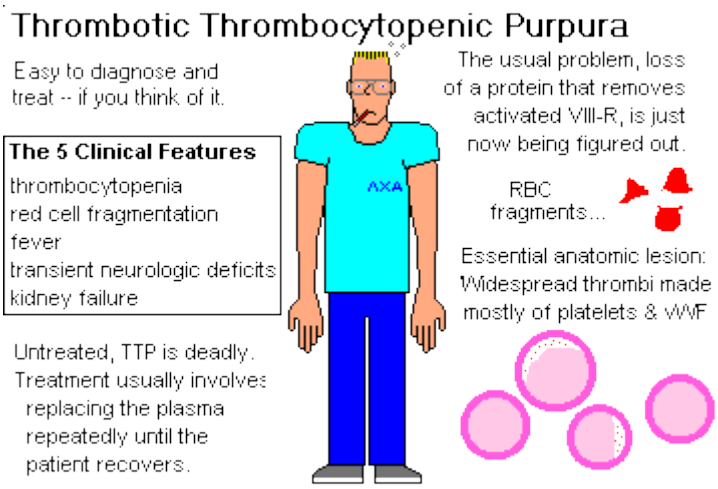
Thrombotic Microangiopathies *(Increased Consumption):*

Due to presence of **mini thrombi that happens all the time** in the blood vessel, it consumes coagulation factors and platelets causing thrombocytopenia and coagulation deficiency.

TTP "Thrombotic Thrombocytopenic Purpura or **DIC** "disseminated intravascular coagulation"

A. **TTP:**

- Deficiency of metalloprotease (**ADAMTS13**) needed for cleaving "HMWK" (usually acquired autoAb against ADAMTS13, but may be inherited)
- Accumulation of HMWK leading to thrombi -> spreading of thrombi in the circulation -> consuming of platelets and coagulation factors -> thrombocytopenia
- Symptoms: Fever, CNS, renal microangiopathic, hemolytic anemia.
- Normal PT, PTT
- Treatment: Plasma exchange.



B. DIC will be mentioned in the end…

ITP vs. TTP vs. DIC

•Parameter	ITP	TTP	DIC
•Pathogenesis	Antiplatelet antibodies	Endothelial defect	Thrombin excess
•Clinical Condition	Not sick	Sick	Sick
•Red Cells	NL	Schistocytes	Schitocytes +/-
•PT (INR)	NL	NL/Slightly Incr.	Incr.
•PTT	NL	NL/Slightly Incr.	Incr.
•Fibrinogen	NL	NL	Decr.
•Fibrin Monomers	NL	Slight Incr.	Incr.
•Fibrin Degradation	NL	Slight Incr.	Incr.
•D-dimers	NL	Slight Incr.	Incr.
•Therapy	Steroids IVIG Splenectomy	Plasma Xchange Vincristine	Rx cause Plasma/Plts ATIII (?)

Hypersplenism -> sequestration:

Trapping of all blood cells and lowering their counts (**Pancytopenia**)

- **Qualitative problems:**

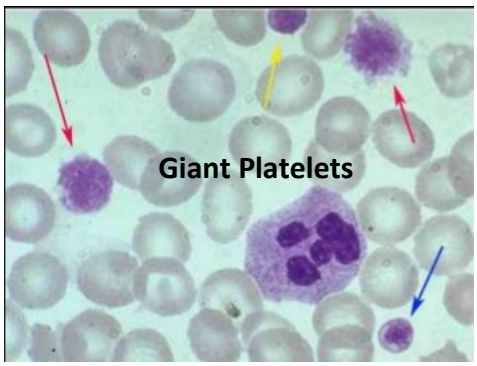
☆ Aspirin is the most common acquired platelet dysfunction

Deficiency of Platelet membrane glycoproteins:

- **GP Ia-IIa: adhesion to collagen.**
- **GP Ic-IIa: laminin receptor.**
- **GP IIb-IIIa: binding to fibrinogen.**
- **GP Ib-IX: adhesion to subendothelial tissue via vWF.**

Deficiency in any one of these glycoproteins leads to a disease,

- **Bernard Soulier syndrome:**
  - **Deficiency of Gp Ib/IX (CD42) which serves as the receptor for vWF.**
  - **Adhesion Defect, Autosomal recessive.**
  - **Giant platelets.**



- **Glanzman's thrombasthenia**
  - **Deficiency of Gp IIb/IIIa (CD41/CD61) which serves as the receptor for fibrinogen.**
  - **Aggregation defect, Autosomal recessive**
  - **Failure to aggregate in response to ADP, collagen, epinephrine and thrombin**

➢ Coagulation disorders:

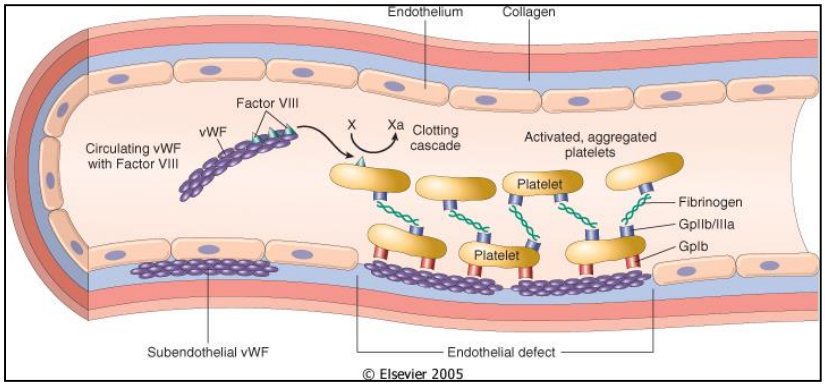
"Congenital or acquired"

Acquired are the most common like:

-- Vit. K deficiency: ⇩ II, VII, IX, X

-- Liver disease (most factors synthesized in the liver)

von Willebrand Factor (vWF):



- **Adhesive protein, bridges collagen to platelets receptor GPIb**
- **It carries and stabilizes factor VIII**
- **Deficiency causes platelet like problem**
- *Coded by a gene located on the short arm of chromosome 12*
- *The primary ptn. product is a 250,000 Da dimer.*
- *Transformed by multiple disulfide bonds to form a series of multimers ranging in weight from 10,000,000 to 20,000,000 Da*

↳ Von willebrand disease type 1:

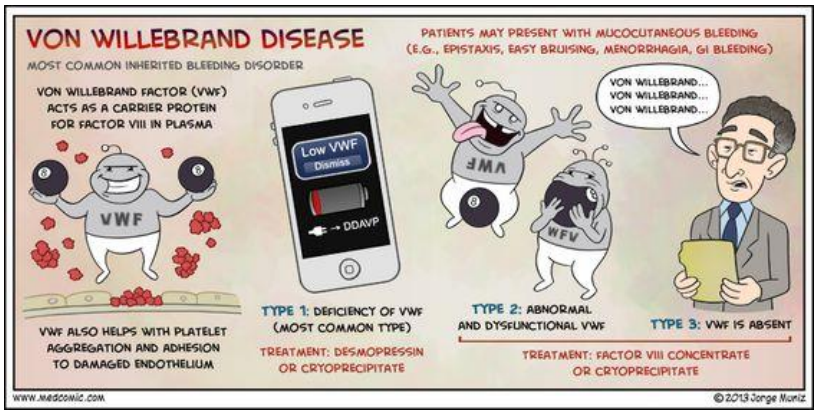
- **Mild deficiency, no symptoms due to sufficient amount of factor VIII**
- **The most common type (75% VWD cases).**
- **Autosomal dominant disorder with variable penetrance (60%)**
- **Reduced circulating vWF and factor VIII.**
- ***All sizes of vWF multimers are present***
- ***Slight prolongation of APTT***
- ***Platelets fail to agglutinate by ristocetin***

↳ vWD Type 2 *"the doctor didn't talk about it"*

- *Reduced circulating large and intermediate multimers of vWF.*
  - *vWF hmw is missing in type A*
  - *vWF has hightened interaction with GP1b in type B*
- *Fctor VIII level is normal.*
- *Failure of agglutination by ristocetin in IIa.*
- *smaller ristocetin doses cause aggregation of platelets in type IIb.*
- *Platelet type VWD is similar to type IIb, but GPIb is defective. Cryo precipitate alone can induce agglutination of platelets*

vWD Type 3:

- **Absent plasma vWF**
- **Markedly reduced factor VIII coagulant activity**
- **Autosomal recessive inheritance**
- **Hemophilia like due to factor VIII deficiency**



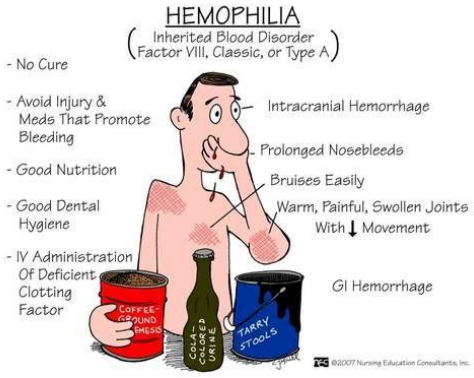
Bleeding in vW disease is similar to bleeding in platelet defects

- **Mucous membrane bleeding(GI bleeding)**
- **Easy bruising**
- **menorrhagia**
- **Post-operative bleeding**

Hemophilias:

Hemophilia A:

- Factor VIII deficiency
- X-linked, rarely affects females and they are usually **carriers**.
- *1/3 of the cases have no family history*
- Caused by absolute reduction of factor VIII or normal amount but defective factor VIII



- **Severity of disease depends on factor VIII level**
  - **Normal level** **100 U/dl**
  - **Severe cases level** **<2 U/dl**
  - **Moderate cases level** **2-5 U/dl**
  - **Mild cases level** **5-25 U/dl**

- **Sites of bleeding:**
  - **Large joints and soft tissue (hemarthrosis in joints and hematoma in muscles)**
  - **Urinary tract and GI tract**
  - **Brain**
  - **Nose**
- **Laboratory tests:**
  - **Prolonged PTT. Normal PT and TT.**
    Remember:(PT is for monitoring oral anticoagulants working on vit k dependent factors, PTT for monitoring Heparin)
  - **Low factor VIII assay**

Hemophilia in Females:

Exceedingly rare, seen in:
- Mating between a carrier mother and affected father
- Carriers with abnormalities of X-chromosome
  - Extreme lyonization
  - X mosaicism or deletion
  - Newly mutant gene

Hemophilia B (Christmas Disease)

- Factor IX deficiency
- X-linked

- **Bleeding sites: similar to hemophilia A.**

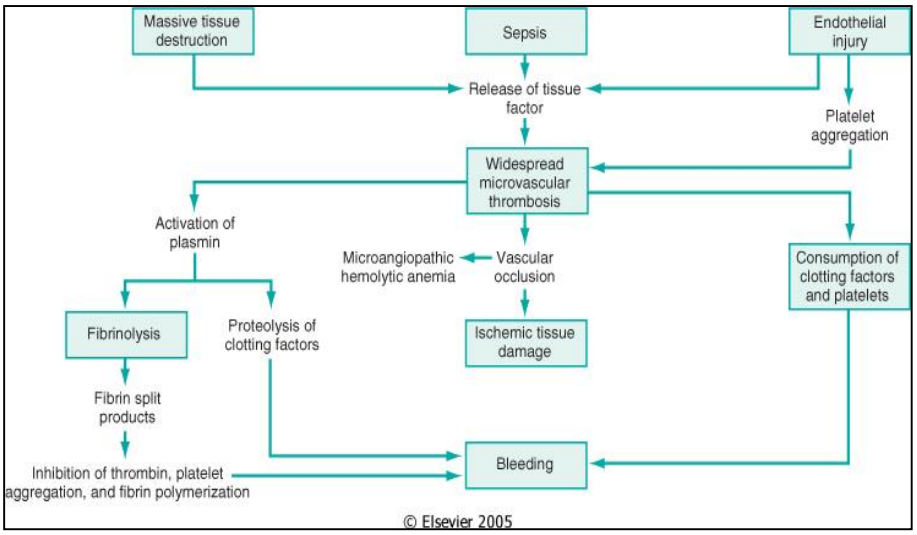
- **Laboratory tests:**
  - **Prolonged PTT. Normal PT and TT.**
  - **Normal factor VIII assay.**

- **Severity of disease depends on factor IX level**
  - **Normal level 100 U/dl**
  - **Severe cases level <2 U/dl**
  - **Moderate cases level 2-5 U/dl**
  - **Mild cases level 5-25 U/dl**

Other factor have their deficiencies but they are very very rare(most common are Hemophilia A & B)

DIC

- Widespread **thrombi** in the microcirculation with secondary **consumption** of platelets and coagulation factors (**consumptive coagulopathy**) which leads to bleeding in the end.
- Mostly caused by **sepsis**, **endothelial damage**, release of **phospholipids** or **TF** form the damaged tissue (damage of tissue due to many reasons like: trauma, toxemia, complication of pregnancy, retained placenta or dead fetus)
- Release of tissue factor or endothelial damage -> activation of extrinsic coagulation cascade and decrease inhibitory pathways



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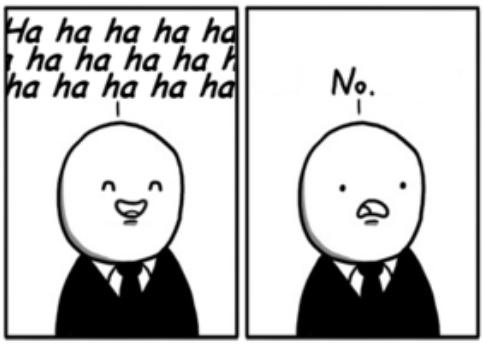

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