THROMBOTIC MICROANGIOPATHIES

Thrombotic Thrombocytopenic Purpura (TTP) and

Pentad of

- Fever
- Thrombocytopenia
- Microangiopathic haemolytic anaemia
- Transient neurologic deficits
- Renal failure

Pathogenesis

DEFICIENCY OF ENZYME ADAMTS 13
(vWF metalloprotease)

↓

High molecular weight polymer of vWF accumulates in plasma

↓

promote platelet microaggregate formation throughout microcirculation

- Microaggregates formation lead to thrombocytopenia, microangiopathic hemolytic anaemia and widespread organ dysfunction.

Hemolytic-Uremic Syndrome

- Microangiopathic hemolytic anemia
- thrombocytopenia
- absence of neurologic symptoms
- the prominence of acute renal failure

Pathogenesis

- Important cause of HUS is infectious gastroenteritis caused by E. coli strain 0157:H7
- Produce shiga like toxin
- It binds to and damages endothelial cells in the glomerulus and elsewhere, thus initiating platelet activation and aggregation

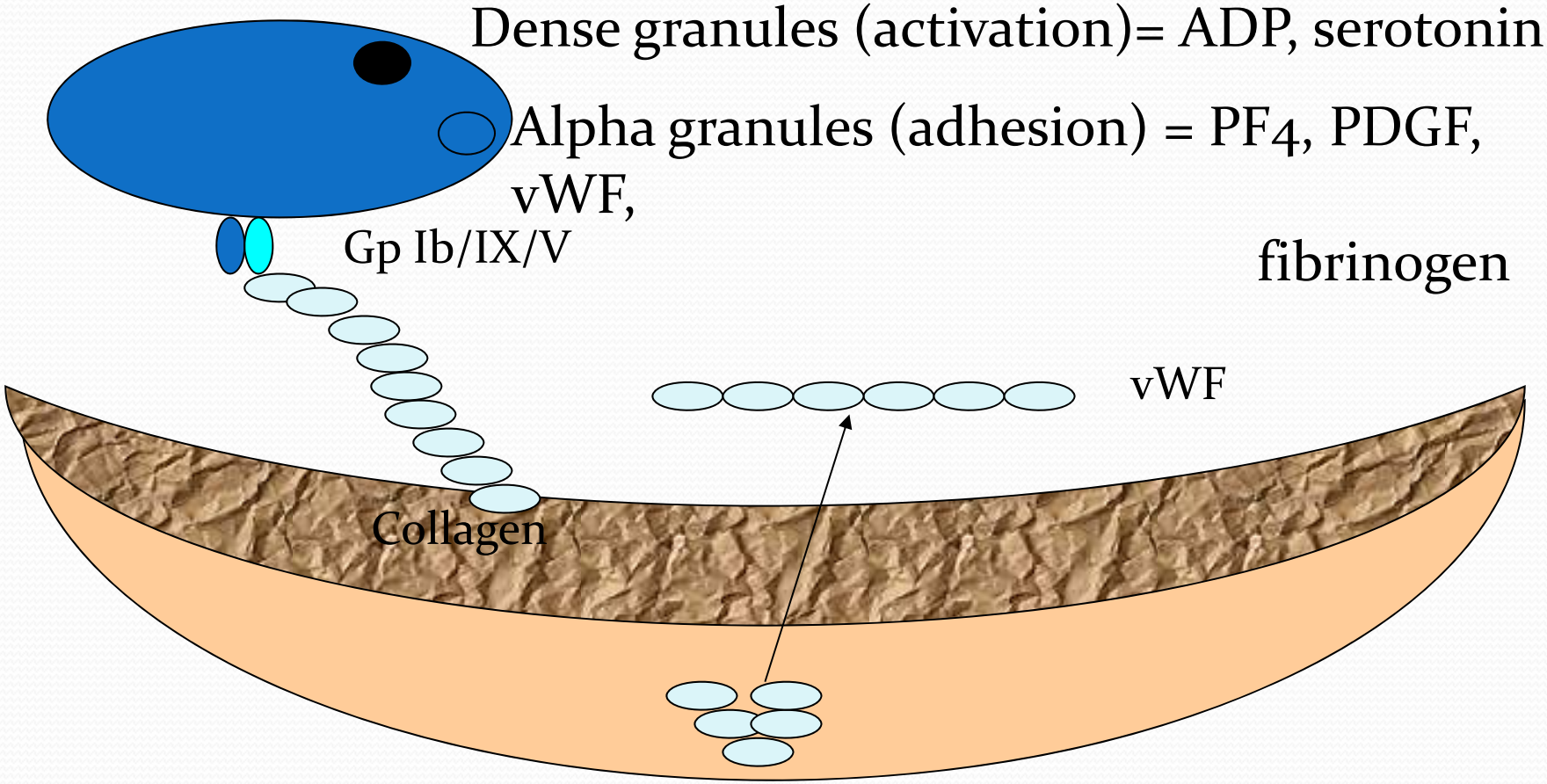
LABORATORY FINDINGS

- Thrombocytopenia.
- Microangiopathic haemolytic anaemia with negative Coombs' test.
- PT and aPTT- Normal
- Bone marrow examination reveals normal or slightly increased megakaryocytes accompanied with some myeloid hyperplasia.
- Diagnosis is established by examination of biopsy - demonstrates typical microthrombi in arterioles, capillaries and venules, unassociated with any inflammatory changes in the vessel wall.

DISORDERS OF PLATELET FUNCTIONS

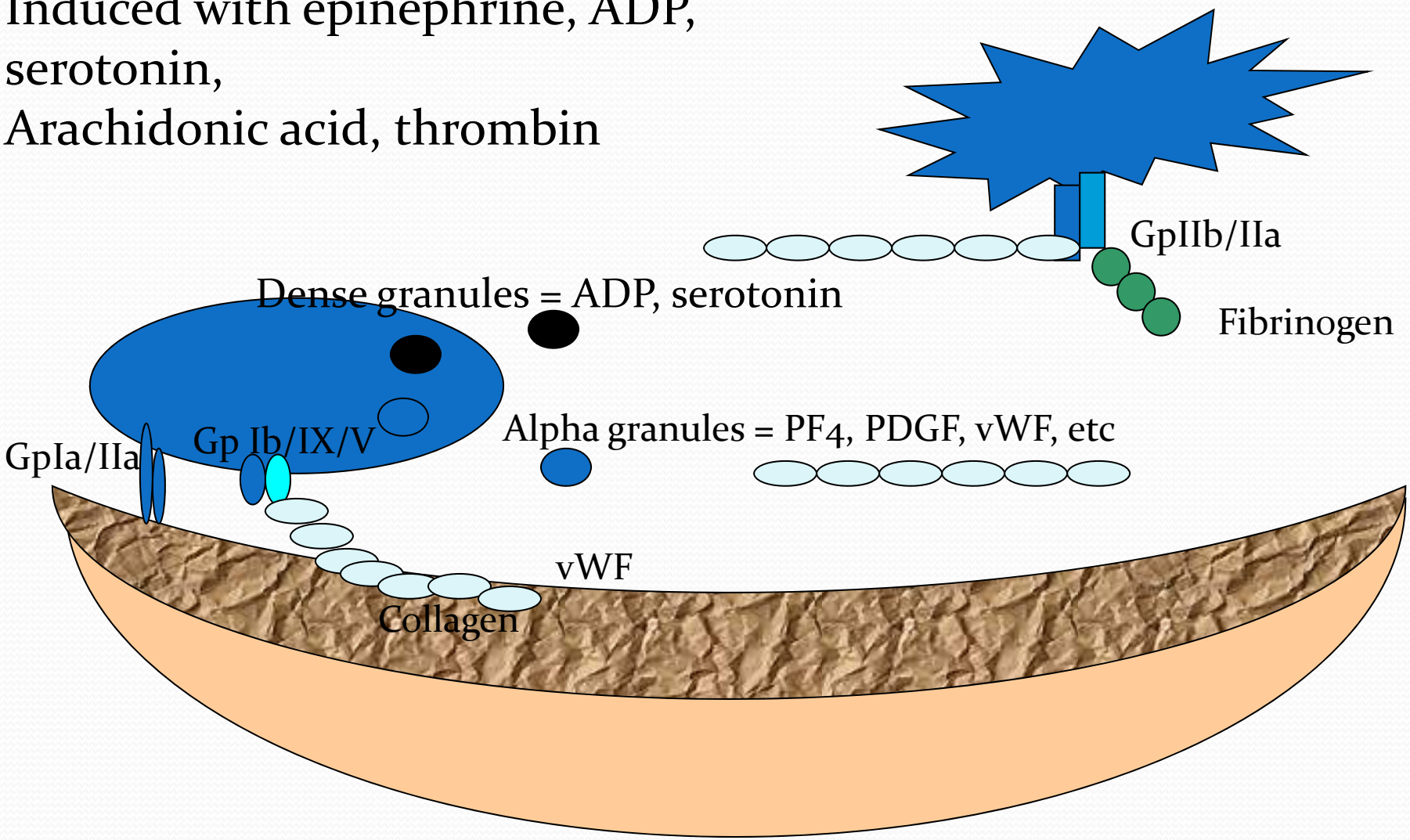
Adhesion

vWF: links PLT to endothelial binding site
PLT receptor GPIb

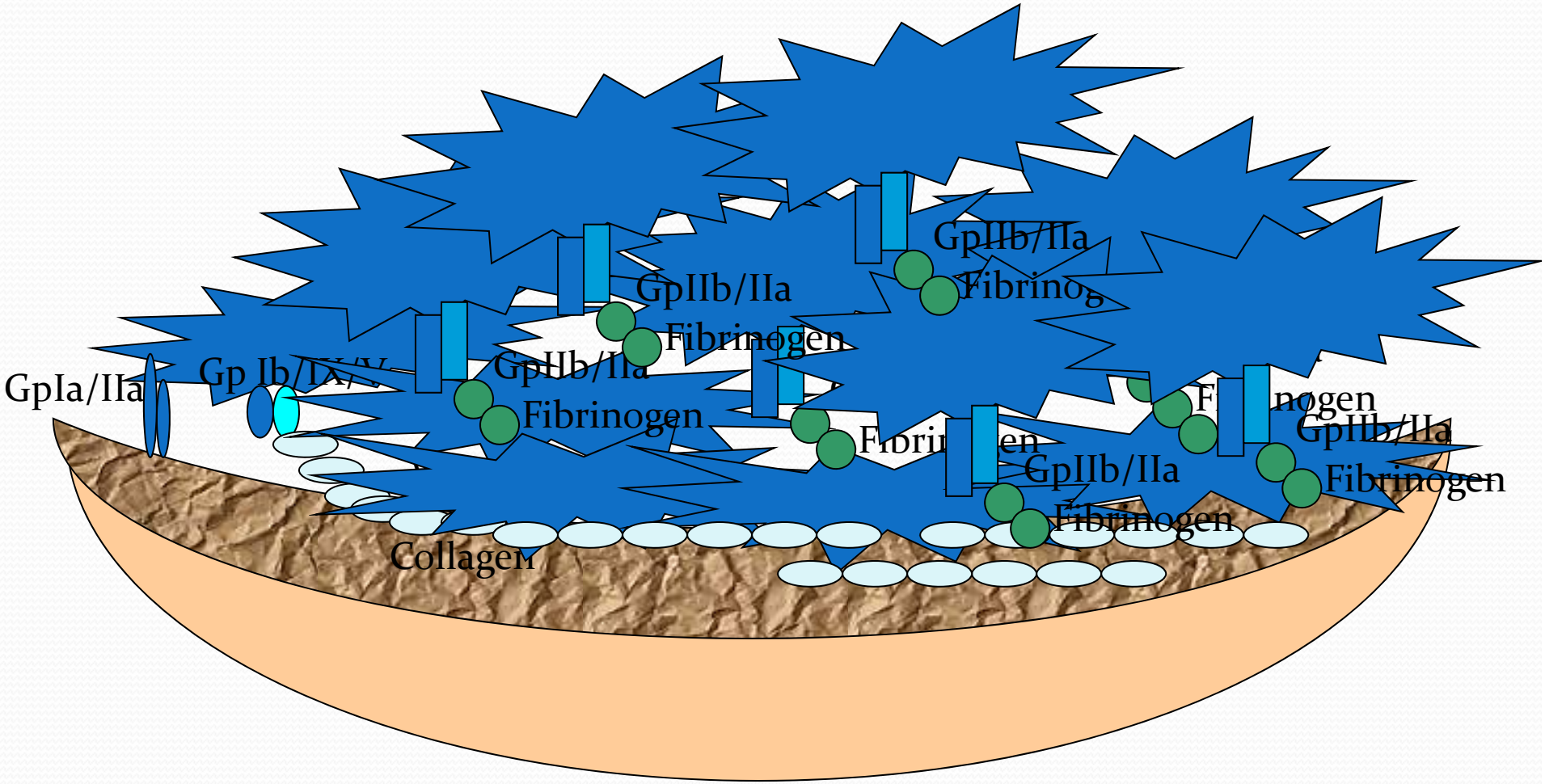


Activation/Release reaction

GpIIb/IIIa conformational change
Induced with epinephrine, ADP, serotonin,
Arachidonic acid, thrombin



Aggregation



Hereditary Disorders

1. DEFECTIVE PLATELET ADHESION:

i) **Bernard-Soulier syndrome-**

- Autosomal recessive
- inherited deficiency of the platelet membrane glycoprotein complex Ib-IX.
- This receptor is essential for binding of platelets to subendothelium via vWF.
- Mild to moderate thrombocytopenia with giant platelets on PBF.
- BT- prolonged, Platelet aggregation impaired with ristocetin and normal with other agonists.

ii) **Von Willebrand's disease**

2. DEFECTIVE PLATELET AGGREGATION

Glanzmann's thrombasthenia

- Autosomal recessive
- Deficiency or dysfunction of glycoprotein gpIIb-IIIa.
- Absence of fibrinogen binding due to lack of receptor –lead to defective platelets aggregation.
- Platelets appear small and discrete on PBF.
- BT- prolonged. Platelet aggregation is absent with ADP, collagen and epinephrine and normal with ristocetin.

3 . DISORDERS OF PLATELET RELEASE REACTION/ STORAGE POOL DEFICIENCY

Dense granule storage pool deficiency:

- Intraplatelet level of ADP, serotonin and calcium are diminished.
- Electron microscopy reveals absence of dense granules

Alpha granule storage pool deficiency:

- Also k/a grey platelet syndrome
- Platelets are mildly decreased in number, larger in size and appear pale grey on PBF

Acquired Disorders

1. ASPIRIN THERAPY

- inhibits the enzyme cyclooxygenase
- suppresses the synthesis of prostaglandins which are involved in platelet aggregation as well as release reaction.

2. Uraemia

3. liver disease

4. Multiple myeloma and Waldenström's macroglobulinaemia

COAGULATION DISORDERS

Hemophilia A (Factor VIII Deficiency)

- due to deficiency or reduced activity of factor VIII (anti-haemophilic factor)
- inherited as a X- linked recessive trait
- manifests clinically in males, while females are usually the carriers
- But excessive bleeding can occur in female also

✓ Heterozygous carrier with lyonisation (inactivation of normal X chromosome.

✓ Turner's syndrome with XO

✓ True homozygous female

Pathogenesis

- Genetic defect are diverse

1. Inversion in F VIII gene at intron 22- most common, detected in 50% of cases.
2. Point mutation
3. Deletion
4. Insertion

Haemophilia A is caused by quantitative reduction of factor VIII in 90% of cases, while 10% cases have normal or increased level of factor VIII with reduced activity.

Clinical Features

FVIII:C level	Type	Clinical Feature
<1%	Severe	Frequent spontaneous bleeding
1-5%	Moderate	Hemorrhage after mild to mod injury
6-50%	Mild	Hemorrhage after major trauma or surgery

Normal Level of FVIII:C is 50-150%

Patient usually present with haemarthrosis and intramuscular hematoma.
Petechiae are characteristically absent.

LABORATORY FINDINGS

1. Whole blood coagulation time is prolonged in severe cases only.
2. Prothrombin time is usually normal.
3. Activated partial thromboplastin time (APTT or PTTK) is typically prolonged.
4. Specific assay for factor VIII shows lowered activity.

Treatment

- Factor VIII concentrate-
  - ✓ Plasma derived
  - ✓ Recombinant
- Cryorecipitate
- Desmopressin- stimulate the release of F VIII and vWF from endothelial cells and platelets.

Hemophillia B (Christmas Disease)

- Inherited deficiency of factor IX (Christmas factor)
- X-linked recessive trait
- PTT is prolonged and the PT is normal, as is the bleeding time.

Treatment:

- Recombinant Factor IX- treatment of choice
- Fresh Frozen Plasma for mild to moderate cases
- Prothombin complex concentrate- for severe cases