Hematology

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Lec. 2

Objectives:

-Define thrombotic thrombocytopenic purpura &hemolytic uremic syndrome?
-Describe platelet function disorders?
-Describe Hemophilia A &B,causes,inhreritance,main feature,diagnosis ?
-Describe Von Willebrand disease (VWD)?
-List the main differences between Hemophilia A and B and Von Willebrand disease ?
-Define thrombophilia and list its causes?

•Thrombotic thrombocytopenic purpura and haemolytic uraemic syndrome

-It results from platelet aggregation in small vessels and is characterised by a pentad of clinical and laboratory features :

Fever ,neurological abnormalities, thrombocytopenia ,microangiopathic haemolytic anaemia and renal impairment.
It is either acquired due to autoantibody or rarely inherited

- There is deficiency of a **ADAMTS13 metalloprotease** which breaks down ultra large von Willebrand factor multimers. (VWF).
- Note: von Willebrand factor VWF promotes platelet adhesion to damaged endothelium

As a result platelets aggregate spontaneously resulting in - microvascular thrombosis that causes variable degrees of tissue ischaemia and infarction and is responsible for the microangiopathic haemolytic anaemia and thrombocytopenia.

-Coagulation tests are normal. -

•Disorders of platelet function:-

Disorders of platelet function are suspected in patients who show skin and mucosal haemorrhage and in whom **the bleeding time is prolonged despite a normal platelet count.** These disorders may be:

***Hereditary*:** rare ,e.g. Thrombasthenia (Glanzmann's disease)
Or
***Acquired*:** aspirin ingestion , uraemia.

3 •Disorders of Coagulation:

•Hereditary coagulation disorders

Hereditary deficiencies of each of the coagulation factors have been described.

Haemophilia A (factor VIII deficiency), haemophilia B (Christmas disease, factor -IX deficiency) and von Willebrand disease (vWD) are the most common.

Haemophilia A (factor VIII deficiency):

-It is the most common of the hereditary clotting factor deficiencies.

-The defect is an ***absence or low level of plasma factor VIII.***

-It is inherited as an X-linked recessive trait, and thus it primarily affects males. However, excessive bleeding has been described in heterozygous females, presumably due to extremely unfavorable lionization (inactivation of the normal X chromosome in most of the cells).

-.There is spontaneous bleeding into **joints &muscles** , disproportionate bleeding following minor trauma or surgery Sometimes gastrointestinal haemorrhage ,haematuria or intracranial haemorrhage.

-**Recurrent painful haemarthroses and muscle haematomas dominate the clinical course of severely affected patients and if poorly treated may lead to progressive joint deformity and disability.**

Laboratory findings :

1. Activated partial thromboplastin time (APTT) is prolonged.
2. . Confirmation is by Factor VIII clotting assay (decrease activity).
   (Mild, moderate ,sever disorder according to the residual Factor VIII activity).
1. The bleeding time ,prothrombin time (PT) and thrombin time (TT) tests are normal.

Factor IX deficiency (Christmas disease, haemophilia B):

The incidence is lower than haemophilia A.
The defect is an ***absence or low level of plasma factor*** **IX**
The mode of inheritance and clinical features of factor IX deficiency are
identical to those of haemophilia A.

laboratory findings :
1. Activated partial thromboplastin time (APTT) is prolonged.
2. Confirmation is by Factor IX clotting assay (decrease activity).
3. The bleeding time, prothrombin time (PT) and thrombin time (TT) tests are normal.

Clinical differences between diseases of platelets/ vessel walls or coagulation factors

Finding	Platelet/vessel walls	Coagulation
Mucosal bleeding	Common	Rare
Petechiae	Common	Rare
Deep haematomas	Rare	Characteristic
Bleeding from skin cuts	Persistent	Minimal
Sex of patient	Equal	>80% male

von Willebrand disease (VWD):

-There is either a reduced level or abnormal function of VWF.
- VWF is a protein produced in endothelial cells and megakaryocytes. It has two roles :
1.) It promotes platelet adhesion to damaged endothelium and
2.) it is the carrier molecule for factor VIII, protecting it from premature destruction. The latter property explains the occasional reduced factor VIII levels found in VWD.

-Usually, the inheritance is **autosomal dominant** , but several rare autosomal recessive variants have been identified.
-There are different subtypes &the severity is variable in the different types.

Typically, there is mucous membrane bleeding (e.g. epistaxes, menorrhagia), excessive blood loss from superficial cuts and abrasions, menorrhagia in females and operative and post-traumatic haemorrhage.

Lab Finding:

1.A prolonged bleeding time.

2•A normal platelet count.

3• The APTT may be prolonged.

4.Factor VIII levels may be low.

5.. The plasma level of active vWF is reduced.

Main clinical and laboratory findings in haemophilia A, haemophilia B, von Willebrand disease..

	Haemophilia A	Factor IX deficiency	von Willebrand disease
Inheritance	Sex-linked	Sex-linked	Dominant (incomplete)
Main sites of haemorrhage	Muscle, joints, post-trauma or postoperative	Muscle, joints, post-trauma or postoperative	Mucous membranes, skin cuts, post-trauma or postoperative
Platelet count	Normal	Normal	Normal
Bleeding time	Normal	Normal	Prolonged
Prothrombin time	Normal	Normal	Normal
Partial thromboplastin time	Prolonged	Prolonged	Prolonged or normal
Factor VIII	Low	Normal	May be moderately reduced
Factor IX	Normal	Low	Normal
VWF	Normal	Normal	Low or abnormal function

• Acquired coagulation disorders:

The acquired coagulation disorders are more common than the inherited disorders. They includes:

1.Disseminated Intravascular Coagulation (DIC) :

Widespread inappropriate intravascular deposition of fibrin with consumption of coagulation factors and platelets occurs as a consequence of many disorders :

Causes of disseminated intravascular coagulation.

1 .Infections

Gram-negative and meningococcal septicaemia

2.Malignancy

3.Obstetric complications

Amniotic fluid embolism

Septic abortion

4.Hypersensitivity reactions

Incompatible blood transfusion

5.Widespread tissue dmnage

Sever trauma***,*** severe burns

*6.****Miscellaneous***

Liver failure, Snake venoms.

Pathogenesis:

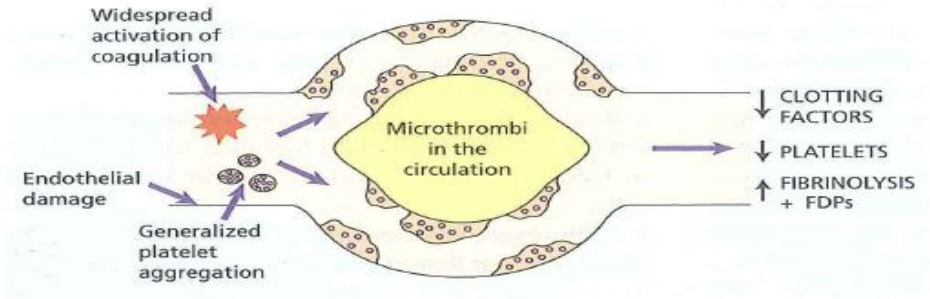
There is systemic activation of the coagulation pathways, leading to the formation of thrombi throughout the microcirculation. As a consequence of the widespread thromboses, there is consumption of platelets and coagulation factors and, secondarily, activation of fibrinolysis.

Thus, DIC can give rise to either **tissue hypoxia and microinfarcts** caused by microthrombi or to a **bleeding disorder** related to pathologic activation of fibrinolysis and the depletion of the elements required for hemostasis .

Two major mechanisms can trigger DIC:

(1) the release of tissue factor or thromboplastic substances into the circulation,e.g. placenta in obstetric complications.

(2) widespread endothelial cell damage***,e.g sever burns.***



Lab. Findings of DIC:

1 .The platelet count is low.

2.Bleeding time is prolonged.

3. Fibrinogen concentration low.
4 .The thrombin time is prolonged.
5 .High levels of fibrin degradation products such as D -dimers are found in serum and urine.
6. The PT and APTT are prolonged .
*7-Blood film examination :*Anaemia and the red cells show prominent fragmentation.

2.Vitamin K deficiency:

Fat-soluble vitamin K is obtained from green vegetables and bacterial synthesis in the gut. Vitamin K is important to perform the final step (γ -carboxylation) in the synthesis of factors II,VII,IX,X.

So ***deficiency of vitamin K*** is associated with a **decrease** in the ***functional activity*** of ***factors II, VII, IX and X and proteins C and S***.

- Deficiency of vitamin K is caused by:

1.) malabsorption .
2.) drugs which act as vitamin K antagonists such as warfarin.
3.) Neonate in the first week of life.

3. liver disease:

1.Since all coagulation factors except VWF are synthesized in the liver, sever liver disease will cause a prolonged PT &PTT.
2.Dysfibrinigenaemia and prolonged TT.
3.Thrombocytopenia due to splenomegally(hypersplenism) which occurs in liver disease.

Thrombophilia

- Some individuals have an increased tendency to venous thrombo-embolism, related to inherited abnormalities of naturally occuring plasma proteins , either anticoagulant proteins or coagulation proteins .This is referred to as " **thrombophilia** ",
- **Inherited causes**: Factor V Lieden gene mutation , Antithrombin deficiency, protein C deficiency ,protein S deficiency.

Thrombophilia also can result from an acquired abnormality e.g. lupus anticoagulant.