Lecture Notes

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PHYSIOLOGY

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019

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Hemostatic Defects

1. Vascular disorder (blood vessels disorder)
2. Platelets' count disorder (Thrombocytopenia) – the most common
3. Platelets' function disorder (Thrombocytopathia)
4. Coagulation factors disorder – the second most common
5. Excessive fibrinolytic system

Vascular Disorder

- The blood vessels become fragile we call it purpura; easily bruised blood vessels, and they easy rupture causing bleeding
- This condition becomes more serious with old age
- Could be inherited or acquired
  - Examples on the acquired type:
    1. Senile purpura: with aging, the blood vessels become fragile due to atrophy of the supporting tissues of the continuous blood vessels. It is seen mainly in dorsal aspects of the forearms and hands
    2. Purpura associated with infection: especially the viral infections
    3. Scurvy: the deficiency of vitamin C
    4. Steroid purpura: associated with prolonged therapy of steroids

Thrombocytopenia

- We said that the platelets maintain the integrity of the blood vessels and when the platelet count decrease, the RBCs leave the capillaries into tissues
- Characterized by spontaneous skin purpura, mucosal hemorrhage and prolonged bleeding after trauma
- Examples for thrombocytopenia:
  1. failure of platelet production
  2. part of general bone marrow failure such as aplastic anemia, leukemia and megaloplastic anemia
  3. increased destruction of platelets such as increase in heparin concentration
  4. abnormal distribution of platelets such as in splenomegaly enlargement of the spleen
  5. dilutional loss in massive transfusion of old blood to bleeding patients

Thrombocytopenic purpura

When the platelet count is low, clot retraction is deficient and there is poor constriction or ruptured vessels. It is characterized by higher susceptibility to bruising (easy bruisability) and multiple subcutaneous hemorrhages.

Thrombocytopathia

- Could be inherited or acquired
  - Inherited: the deficiency in any component of the contents of the platelets such as factor eight VWF, release of ADP, serotonin, granules, or failure to produce from thromboxane A_2 then failure to aggregate
  - Acquired: example the aspirin therapy

Thrombasthenic purpura

Purpura may also occur when the platelet count is normal and in some of these cases the circulating platelets are abnormal and then also the blood vessels become fragile when the platelets' function is abnormal

Coagulation factors disorder

- Inherited deficiencies of most of the coagulation factors have been described
- Hemophilia A/factor 8 deficiency, hemophilia B/Christmas disease/factor 9 deficiency and Von Willebrand's disease are uncommon. The rest of the deficiencies are **rare**.

TABLE 32–7 Examples of diseases due to deficiency of clotting factors.

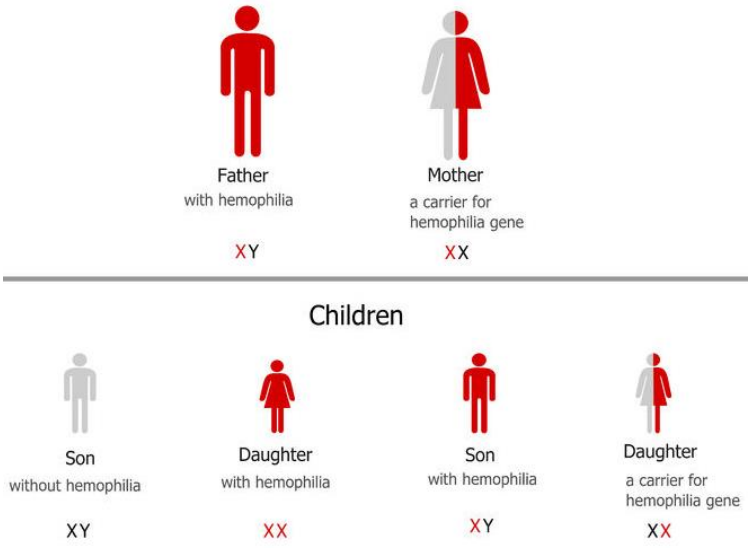
Deficiency of Factor:	Clinical Syndrome	Cause
I	Afibrinogenemia	Depletion during pregnancy with premature separation of placenta; also congenital (rare)
II	Hypoprothrom-binemia (hemor-rhagic tendency in liver disease)	Decreased hepatic synthesis, usually secondary to vitamin K deficiency
V	Parahemophilia	Congenital
VII	Hypoconvertinemia	Congenital
VIII	Hemophilia A (classic hemophilia)	Congenital defect due to vari-ous abnormalities of the gene on X chromosome that codes for factor VIII; disease is there-fore inherited as sex-linked characteristic
IX	Hemophilia B (Christmas disease)	Congenital
X	Stuart–Prower factor deficiency	Congenital
XI	PTA deficiency	Congenital
XII	Hageman trait	Congenital

Hemophilia A - factor 8 deficiency

- The most common inherited coagulation defect among the uncommon defects
- Incidence 1:10000
- The defect is an absence or low level of factor 8
- Sex-linked, but 33% of patients don't have a family history

The defect on chromosome X. therefore,

- A hemophiliac male has $\bar{X}$ **Y (**$\bar{X}$ Has the defect)
- A female carrier $\bar{X}$**X**
- A hemophiliac female $\bar{X}\bar{X}$ (she does not survive because that defect is in both chromosomes)
- When a hemophiliac male gets married to a carrier woman: two-fourth diseased (hemophiliac), one-fourth carrier, and one-fourth normal (see the figure)



Remember factor VIII is either VWF for adhesion or related antigen (R:Ag) for the aggregation and C for clotting

In normal individuals:

- Factor VIII:C and VIIIR:AG circulate bounded in the plasma

In Hemophilia A:

- Part C is deficient on chromosome X
- Somatic chromosomes have factor VIII related antigen normal
- The result: factor VIII related antigen only, <u>coagulation is defective</u>

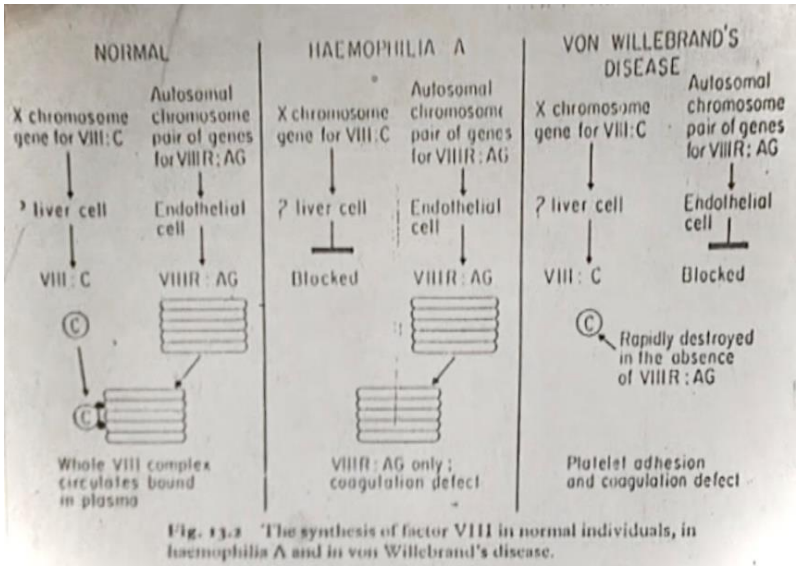


Fig. 13.2 The synthesis of factor VIII in normal individuals, in haemophilia A and in von Willebrand's disease.

In Von Willebrand's disease:

- The problem is in the somatic chromosome
- C is normal
- Related antigen is abnormal
- The result: factor VIII C is rapidly destroyed in the absence of related antigen. Therefore, <u>platelets adhesion and coagulation are defeated</u>

Main clinical and laboratory findings in haemophilia A, factor IX deficiency (haemophilia B, Christmas disease) and von Willebrand disease.			
	Haemophilia A	**Factor IX deficiency**	**Von Willebrand disease**
Inheritance	Sex-linked	Sex-linked	Dominant
Platelet count	Normal	Normal	Normal
Bleeding time	Normal	Normal	Prolonged
Factor VIII:C	Low	Normal	Low
Factor VIII:AG	Normal	Normal	Low
Aggregation	Normal	Normal	Impaired

Clinical features: Severely affected infants may suffer from profuse post-circumcision hemorrhage. Prolonged bleeding occurs after dental extraction. Operative and post traumatic hemorrhage are life threatening in both severely and mildly affected patients.

Hereditary disorders of other Coagulation factors:

1. All these disorders are rare other than hemophilia A, b, Von willbrand
2. Most inheritance is autosomal (somatic)
3. There is usually a good correlation between the patient's symptoms and the severity of the coagulation deficiency
4. Factor XII (12) deficiency is not associated with abnormal bleeding
5. Factor XI (11) deficiency produces mild symptoms (sometimes could be severe)
6. Factor XIII (13) deficiency produces severe bleeding because fibrin threads are not stabilized

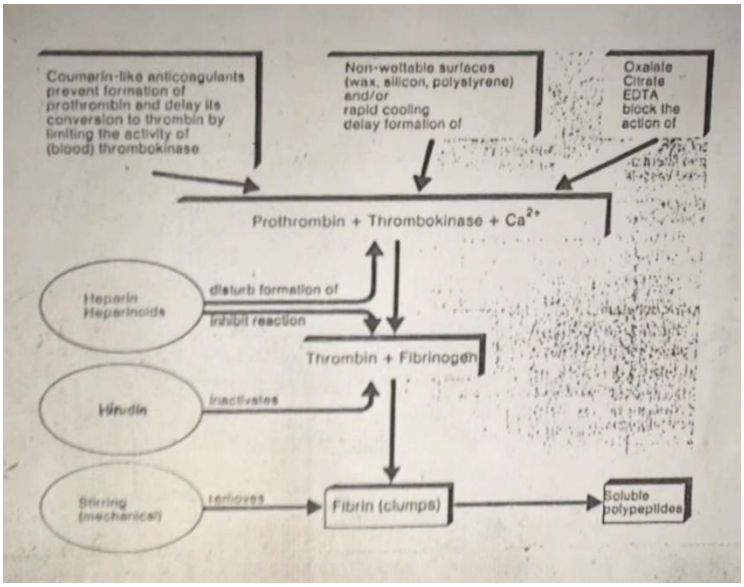
Anticoagulants

Anticoagulants are chemicals that prevent & inhibit the coagulation mechanism, used in labs and for clinical use

- Coumarin-like or Warfarin-like anticoagulants: prevent the formation of prothrombin and delay its conversion to thrombin by limiting the activity of blood thrombokinase formation.
- Non-Wettable surfaces (wax, silicon, or polystyrene) and/or rapid cooling: delay formation of thrombokinas
- Oxalate, citrate, & EDTA: block the action of Ca2+
- Heparin produced by basophils, it disturbs the formation of thrombokinase and it inhibits the reaction between thrombin and fibrinogen.
- Hirudin produced by the leech, it inactives thrombin formation
- Stirring (mechanical method), removes the fibrin (clumps)

Generally, the anti-coagulant is either EDTA usually or heparin or warfarin or Coumarin

	Heparin	Warfarin
Origin	animal origin	plant origin
Onset	acts rapidly	acts slowly after one to two days
Duration of action	Hours	Days
Mechanism of action	It inactivates the whole intrinsic pathway	Acts on 2 7 9 10; the vitamin K dependent factors
Activity	In vivo and in vitro	In vivo only
Route		given orally



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