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Histology

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Sheet 9

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lecture number :

9

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"Platelets and clotting factors disorders"

In this lecture the dr. discussed bleeding tendency diseases (Hemophilia), then the thrombotic diseases (Thrombophilia).

*** Bleeding tendency:**

1- Hemophilia A:

- It is a genetic disease results in deficiency of clotting factor VIII , which is normally involved in the intrinsic pathway of coagulation.

- It is inherited as an X-linked recessive trait, so it is more common in males. There is family history in 70% of cases , while in the other 30% of cases it arise from new spontaneous mutation then it's transmitted latter to the off-springs . When asking about the family history we mostly ask about the maternal uncle, because he has 1X chromosome and most likely he is carrying the mutation, while the sister of the mother could be a silent carrier.

-We use a special test that measure the functionality of the intrinsic pathway, called the "PARTIAL THROMBOPLASTIN TIME or PTT" >> In normal blood sample, the coagulation occurs after 10 sec., but in hemophilia A, it will be prolonged, because there is no enough factor VIII (part of intrinsic pathway).

*** Pathogenesis:**

The mutation in this disease results either from:

1. Quantitative deficiency (in 90% of cases)
2. Qualitative (in 10% of cases)

- Normally, there is a large reserve of factor VIII in normal person; we can take around 50% of the amount, and the person remains asymptomatic. The symptoms of hemophilia A start to appear when the level of factor VIII drops to about 10% of normal amount, after this the patient will have tendency for bleeding. Hemophilia is like any other disease, the mutations vary > it is not single or identical in all patients. Some patients have a bad mutation where the amount of factor VIII is very low (around 1% only) so those patients will suffer from severe symptoms and spontaneous bleeding even without trauma.

Other patients may have (around 10% of the factor), so they have bleeding when there is trauma or physical activity.

* Clinically, the bleeding occurs in deep sites (like the trunk or the joints) not superficial (in skin), and this is a characteristic of *clotting factor deficiency*, in contrast to *platelet deficiency or abnormality*, where the bleeding tend to be superficial.

* In clotting factor deficiency, the bleeding manifests in deep organs such as the trunk or the joints, so these patients commonly have joint bleeding which is acute at the beginning, then a large amount of blood accumulate in the joint and with chronic bleeding this joint becomes deformed.

- Hemophilia "A" manifest during early life "at the time of circumcision".

2- Hemophilia B:

-It is very similar to hemophilia A, but the factor that is deficient here is clotting factor IX , which is also involved in the intrinsic pathway.

-It's also inherited as an X-linked recessive, so there's family history of maternal uncle and it's very similar clinically to hemophilia A.

-PTT test is also prolonged.

*Generally we diagnose Hemophilia A and B by doing a test called "Mixing study test" where we bring a blood from a patient and mix it with normal healthy plasma (i.e. plasma with normal levels of clotting factors) > then we do PTT test on the mixed blood. In hemophilia patients the PTT test will be corrected after adding the normal plasma, because the deficient factor is added. And if we want to go further and know whether it is factor VIII or IX deficiency, we do special enzymatic test called the factor essay.

* **Treatment**: of both hemophilia A or B is by giving the patient regularly normal plasma.

** There is an acquired autoimmune disease where auto-antibodies are synthesized against clotting factors, mainly factor VIII. In this case if we added normal plasma to the patient's blood (i.e. performing the mixing study test), the PTT will not be corrected.

→ So mixing study test is important to differentiate between inherited and acquired hemophilia.

3- Von Willibrand disease:

{Normally VWF has two binding sites for factor VIII in circulation , and also it is found beneath the endothelium bound to collagen of blood vessels . In the case of endothelial injury, the VWF will act as a receptor for platelets that binds to them forming a plug}
-VW disease causes deficiency of VWF, thus any trauma to the blood vessels will cause bleeding, and since the VWF carries factor VIII, any deficiency in VWF will cause factor VIII deficiency.

- It is an **autosomal dominant** disease, and **it's the most common type of hemophilia.**

* Clinically it is milder (less severe) than hemophilia A and B, and it has two types:

1. Quantitative (VWF is absent)
2. Qualitative (abnormal shape, so that it binds platelets abnormally in the circulation >> so it can cause thrombocytopenia in addition to bleeding tendency)

- Since the VWF carries factor VIII so when there's VWF deficiency, factor VIII will be deficient; thus patients will have prolonged PTT (due to factor VIII deficiency) and sometimes prolonged bleeding time, which measures the platelets function (secondary to thrombocytopenia).

So we have 3 tests:

1. PTT measures the functionality of the intrinsic pathway.
2. PT test measures the functionality of the extrinsic pathway.
3. Bleeding time evaluates the platelets' function.

In this disease there's prolonged PTT (secondary to the loss of factor VIII) and prolonged bleeding time (in the qualitative one, secondary to thrombocytopenia).

Idiopathic thrombocytopenic purpura (ITP)

Idiopathic: [With unknown cause], thrombocytopenic: [Decreased platelet count], purpura: [Special type of bleeding in skin].

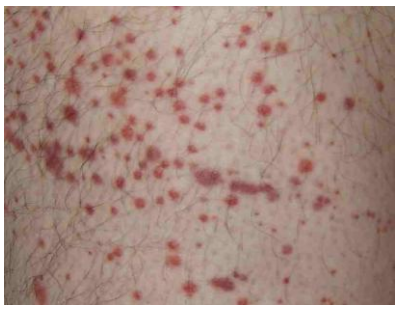
-It is acquired, autoimmune disease where the body synthesizes auto-antibodies of IgG type against glycoprotein IIb/IIIa, which is normally present on platelet surface.

* Clinically there are 2 settings of the disease:

a. Acute: common in children, post viral infections due to molecular mimicry where some viruses have proteins with structures similar to the structure of glycoprotein IIb/IIIA so when the body fights the virus there's a cross binding (the antibodies fights the virus as well as the platelets).
b. Chronic: common in older ages, mostly in females. It's an autoimmune disease that cause derange in normal function of TH cells (TH cells increase in number and function causing activation of B-cells that secret abnormal Ig –mainly IgG – against platelets). Chronic ITP occurs also in persistent infections such as (HIV, H-pylori, and HCV).

***Pathogenesis and Morphology of ITP:**

a. molecular mimicry (in acute ITP)
b. Deranged "abnormal" immune system.
c. High TH1 count and function → lead to activation of B-cells →thus secreting IgG that binds to platelets membrane GP → then the AB-coated platelets induce Fc receptor mediated phagocytosis by microphages mainly in spleen, causing **splenomegaly** and **thrombocytopenia**.
d. Activation of megakaryopoiesis in bone marrow → the bone marrow is normal because this disease involves peripheral destruction (like hemolytic anemia, the BM is normal), so there's a large no. of megakaryocytes in the BM, but they are totally normal.
e. Increased immature platelets production, and they're released from the BM as large immature cells; so in peripheral blood, the platelets look large (immature).
f. Bleeding secondary to platelet deficiency manifest more commonly in superficial parts (skin) and it's called purpura (pinpoints bleeding that is palpable)



* Microangiopathic hemolytic anemia:

-Consist of 3 diseases (Thrombotic thrombocytopenic purpura, Hemolytic uremic syndrome, Disseminated intravascular coagulation)

1) Thrombotic thrombocytopenic purpura (TTP):

-It's caused by a mutation "abnormality" or deficiency in protein called (ADAMTS13).

- In 90% it's acquired due to auto-antibodies that inhibit this protein and it's commonly of IgG type, in this case it's a temporary disease that can be resolved or treated. BUT in 10% it's inherited as autosomal recessive causing deficiency in (ADAMTS13) protein.

*What is the normal function of ADAMTS13?
-its function is to produce the VWF from its precursors

* The deficiency of ADAMTS13 causes the appearance of large multimers (precursors of VWF) → these multimers are potent and they bind to platelets causing microcirculatory occlusion. The increased binding of platelets → causes wide spread thrombosis, then thrombocytopenia → thus secondary bleeding.

- In this disease the (PT + PTT) are normal (because the clotting factors are not affected); however, the bleeding time is prolonged (due to thrombocytopenia).
(NOTE: Prothrombin time (PT): measures the functionality of the extrinsic pathway of coagulation)

*The clinical features of the disease:

1. Hemolytic anemia → thrombosis causes physical damage to the RBCs which appears as broken RBCs and referred to as schistocytes.
2. Thrombocytopenia → due to increased binding of multimers to the platelets causing platelet deficiency.
3. Renal failure → secondary to infarction.
4. Neurological symptoms.
5. Fever.
6. Systemic inflammation.
7. Purpuric rash.

2) Hemolytic uremic syndrome :

-It's common in children, results from an infection of one of the serotypes of E.coli {O157:H7} → which causes hemorrhagic diarrhea and also secretes Shiga-like-toxin that circulate in blood causing wide spread physical damage to endothelium and that cause secondary bleeding.

So at the end it is similar to the previous disease but the MECHANISM is different.

* This disease mainly causes severe damage to the kidney (more than TTP), because the glomeruli have many receptors for the shiga-like-toxin. So, renal failure is prominent in patients with HUS. Thus it's called UREMIC.

- We also see marked schistocytes because of the hemolytic anemia.

- The patient will have prolonged bleeding time (secondary to thrombocytopenia), but normal PT and PTT.

3) Disseminated intravascular coagulation:

- It's the most common of the microangiopathic diseases.

- It's an acquired disease, caused by the activation of coagulation system (all the clotting factors will be severely activated) → leading to wide spread thrombosis … After that the anti-coagulation system with all its factors will be activated → they will lyse all these thrombi → ending with bleeding.

So, (it is thrombosis due to activation of clotting factors, followed by bleeding due to activation of anti-coagulation factors)

- There is prolongation in all the three tests (PT + PTT +BT), it's an important info. to differentiate between DIC and the other 2 diseases.

* The causes of DIC:

a. Cancers (commonly mucinous carcinoma ex: adenocarcinoma).
b. Acute promyelocytic leukemia (tissue factor secretion).
c. Sepsis (due to tissue factors + endotoxins).
d. Severe inflammation.
e. Head trauma (due to tissue fragments of the brain that circulate in the blood).
f. Labor (fragments of placenta act as foreign bodies).
g. Wide spread endothelial damage (ex: snake venom, heat and burn).

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* *Acquired bleeding disorders:*

They are more common and caused by:

1. Chronic liver diseases (because the liver synthesize the clotting factors).
2. Vitamin K deficiency (because it's important in the function of some clotting factors {factor 2, 7, 9, 10} that are used in coagulation pathways).
3. Warfarin (it's an anti-thrombotic drug that inhibits the vit. K dependent factors).
4. Aspirin (it inhibits the synthesis of thromboxane A2 so inhibits platelet aggregation, platelet count is normal but they're not functioning thus prevent thrombosis).
5. Microangiopathic hemolytic anemias (TTP, HUS and DIC).

Now we come to the second group of disorders, the Thrombophilia

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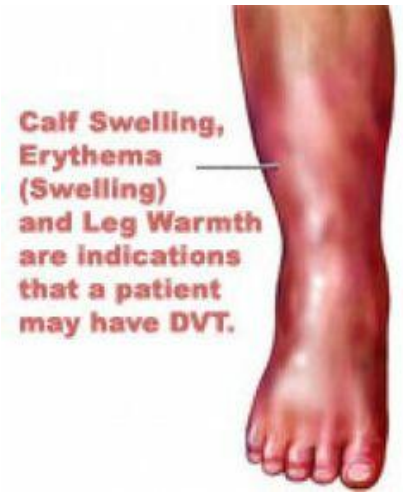
* Thrombophilia: (tendency for thrombosis)

- Most of the diseases are acquired, such as:

1. Thrombocytosis: increased number of Platelets → platelet aggregation → thrombosis formation. We took this in myeloproliferative neoplasms and the most common are primary myelofibrosis and essential Thrombocythemia where pateients have recurrent thrombosis.
2. Polycythemia Vera: it's a myeloproliferative neoplasm but it is secondary to large no. of RBCs, the RBCs themselves form thrombus.
3. Sickle cell anemia: RBCs physically bind to each other forming thrombus.
4. PNH: patients have thrombocytopenia but when the platelets lyse, they secrete their contents causing thrombosis.
5. antiphospholipid syndrome: it's very common, acquired autoimmune disease with multiple Abs; some of these Abs block protein C or S and some activate prothrombin. It's not corrected by mixing study test because the Ab is there.
6. Pregnancy (due to hormonal changes leading to increased thrombin).
7. Some drugs (most commonly Oral Contraceptive Pills)

- Inherited diseases include:



1- Factor Leiden (V) deficiency: it's the most common, autosomal dominant; the mutant factor (the factor is not deficient, it's mutated) is resistant to lysis by protein C, so if it's there it will keep functioning → persistent activation of thrombin → resulting in thrombosis.

2- Factor II (prothrombin) mutation:
mutation leads to prolonged function of this factor → leading to thrombosis.

3- Protein C and S deficiency:
they both work on factor V, so if they are deficient, factor V will keep working → causing thrombosis.

* Last thing in this lecture is the DVT (deep vein thrombosis):

- It's a clinical condition, not a pathological one. Deep vein thrombosis (DVT) is usually the formation of a thrombus in the deep veins of the lower limbs secondary to slow circulation or prolonged immobility.

- 50% of patients of DVT have previous history of thrombosis.

- Limbs appear swollen, red and painful.

- There is a chance for these thrombi to separate → and move to the lungs→ blocking the venous system → causing failure and sudden death.

Success is not final, failure is not fatal: it is the courage to continue that counts.

Sorry for any mistake ^_^

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