Doctor.021

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HLS PATHOLOGY

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Before I start, Anything written in black is the doctor's speech and my notes
Anything written in purple is the doctor's slides

And now let's start:

BLEEDING DISORDERS

In this lecture we are going to talk about syndromes and diseases that are categorized as "Bleeding disorders" :

1- DISSEMINATED INTRAVASCULAR COAGULATION (DIC)
2- THROMBOTIC THROMBOCYTOPENIC PURPURA (TTP)
3- HEMOLYTIC UREMIC SYNDROME (HUS)
4- VON WILLIBRAND DISEASE
5- HEMOPHILIA A
6- THROMBOCYTOPENIA with 2 related diseases:
   A) IMMUNE THROMBOCYTOPENIC PURPURA
   B) HEPARIN-INDUCED THROMBOCYTOPENIA

Firstly, What do we mean by abnormal bleeding?
It is defined as spontaneous bleeding or prolonged bleeding after trauma (without injury).
Caused by abnormality in:
1) platelets
2) clotting factors
3) structure of blood vessels – endothelial cells
or a combination between these causes.

Before we proceed, let's talk about bleeding secondary to "FRAGILE BLOOD VESSELS" :
fragile blood vessels occur in certain situations:

▪ the use of high corticosteroid like cortisol, as a treatment of dermatology diseases or in case of Cushing's syndrome (which is a disorder that occurs when your body makes too much of the hormone cortisol over a long period of time) then we will have weak blood vessels as a result of high cortisol.

▪ Scurvy (vitamin C deficiency) (it occurs in old ages because of scarcity of vitamin c in food) (vitamin c is important for collagen structure in blood vessels)

▪ Vasculitis (autoimmune or infectious) (inflammation of blood vessels)

▪ Inherited disorders of connective tissue (and this leads to weak connective tissue tends to bleed)

so in this situation, Patients develop spontaneous petechiae(small bleeding in the skin and superficial areas) and ecchymoses(large bleeding area, bruises) in skin and mucous membranes (may occur in the eye and conjunctiva because of ruptured small capillaries)

Laboratory tests of platelets and clotting factors are normal (because the problem is in the blood vessel itself)

Now, let's talk about the diseases we have mentioned before :

1- DISSEMINATED INTRAVASCULAR COAGULATION (DIC) :
▪ in this disease , there will be systemic activation of coagulation system in the body
▪ then, formation of myriads of thrombi in the microcirculation(small capillaries

and arterioles), and this may cause ischemia and microinfarction
▪ Followed by activation of fibrinolysis (firstly, formation of thrombi and then they are dissolved)
▪ Then patients become at risk of severe bleeding (because of consumed platelets and clotting factors in the formation of these thrombi)
▪ And as a consequence, patients develop thrombocytopenia, anemia and schistocytes (mechanical damage anemia (micro angiopathic anemia), the RBCs are destroyed and become schistocytes when they move through these thrombi)

so in this disease :
1- formation of thrombi and as a consequence consumption of all clotting factors and platelets in these thrombi
2- when these thrombi are dissolved, the patients become at risk of bleeding

so initially there is an infarction, but then it turns to a risk of bleeding (this is called consumptive coagulopathy) , and in this disease patients are at risk of death , emergency disease.

Pathogenesis occurs in one of either 3 mechanisms:
1) Release of tissue factor into the circulation (and this activates the extrinsic pathway) > formation of thrombi
2) Widespread endothelial damage (causes release of tissue factor (secondary activation of extrinsic pathway) and expose the subendothelial von Willebrand factor) > platelet aggregation and formation of thrombi
3) In physical damage of tissues there will be a release of negatively charged substances in the circulation (activates intrinsic pathway) > formation of thrombi

1) HIGH TISSUE FACTOR RELEASE :
what are the diseases that are associated with high release of tissue factor?
▪ From placenta, in obstetric complications (complications in the placenta like bleeding in placenta, death of the baby and leak of amniotic fluid, result in

release of tissue factor)

▪ From certain cancer cells (acute promyelocytic leukemia (APL) (malignant blasts release tissue factor in the blood, kills the patient because of bleeding rather than the tumor itself), adenocarcinoma(release of myosin from malignant cells that circulates in the blood > activation of tissue factor > DIC (pancreatic carvinoma > DIC))

▪ Bacterial sepsis, bacterial toxins activate TF on monocytes(1), also monocytes secrete tumor necrosis factor and IL-1 that stimulate expression of TF on endothelium and inhibit thrombomodulin(2) (the function of thrombomodulin is inhibition of thrombosis)

both pathways (1,2) end up with tendency to form thrombi in the circulation

these I have mentioned are complications associated with DIC because of high release of tissue factor .

2) WIDESPREAD ENDOTHELIAL DAMAGE:

seen in several diseases:

▪ Deposition of antigen-antibody complexes (systemic lupus erythematosus, vasculitis(autoimmune diseases)) (autoimmune disease > formation of self Ag-Ab complexes > deposition of these complexes on endothelial cells which causes damage > DIC)

▪ Severe heat exposure (heat stroke, burn injury) (endothelial damage > DIC)

▪ Snake venom (direct damage of endothelial cells > DIC)

▪ Certain infections (meningococci(caused by Neisseria meningitidis), rickettsiae, COVID19), this condition is called systemic inflammatory response syndrome (certain infections > severe inflammation > causes endothelial damage > DIC)

3) ACTIVATION OF INTRINSIC PATHWAY :

occurs with :

▪ Massive physical tissue damage (trauma, surgery) > activation of intrinsic

pathway > can develop DIC

- Head injury > activation of intrinsic pathway > can develop DIC
- Brain substance and collagen are negatively charged particles that are released in blood > activation of intrinsic pathway > can develop DIC

CLINICAL AND LABORATORY FINDINGS :

- Thrombocytopenia (consumptive coagulopathy > decreased platelets > thrombocytopenia), prolonged PT and PTT (consumptive coagulopathy > decreased clotting factors > prolonged PT and PTT), schistocytes (seen in the blood smear)
- Acute DIC (e.g. obstetric complication) shows ecchymosis(and petechiae), severe hemorrhage into body cavities (superficial and deep bleeding > shock and death)
- Chronic DIC (e.g. cancer related) shows recurrent thrombosis (the clinical picture shows that the patient suffering from ischemic impact (because it is chronic))
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- Waterhouse-Friderichsen syndrome : meningococcus sepsis → DIC → adrenal hemorrhage → acute adrenal failure (no steroids > hypotension) (necrosis of adrenal glands because of bleeding which causes tissue damage)
- Sheehan syndrome: complicated labor → DIC → severe hemorrhage → pituitary ischemia and necrosis and as a consequence :

- loss of the pituitary hormones
- loss of blood pressure
- loss of lactation because of decreased prolactin which is secreted from the pituitary

(2,3) THROMBOTIC THROMBOCYTOPENIC PURPURA (TTP) & HEMOLYTIC UREMIC SYNDROME (HUS): (2 similar diseases)

▪ Widespread formation of platelets-rich thrombi in microcirculation (like the DIC but in a different mechanism > (normal PT and PTT))
▪ NO activation of clotting factors (normal PT and PTT) (the clotting system is preserved)
▪ Leads to thrombocytopenia and tendency for bleeding (can be fatal)
▪ Clinically: fever, thrombocytopenia, microangiopathic hemolytic anemia(there is schistocytes), renal failure and neurologic symptoms (the latter (neurologic symptoms) not present in HUS) (5 symptoms for TTP and 4 for HUS)

in these 2 diseases, patients have a risk of bleeding, but the clotting factors are preserved and the bleeding occurs as a result of thrombocytopenia

2- TTP :

▪ Congenital or acquired (acquired more common)
▪ Deficiency in metalloproteinase ADAMTS13, normally controls vWF production (metalloproteinase ADAMTS13 is responsible for the production of vWF which is important for the formation of thrombi (platelet rich thrombi))
▪ ADAMTS13 normally cleaves the precursor of vWF (large multimer molecule) into vWF. This multimer is capable of binding multiple platelets causing thrombosis

for clarification: vWF is responsible for the formation of platelet rich thrombus in the normal way for the circulation, and this vWF is produced by the fragmentation of the precursor of vWF by ADAMTS13, but when there is a deficiency of ADAMTS13 this precursor stays as a large multimer molecule and the it binds a lot of platelets in a way higher than the normal vWF and thus there will be thrombosis

3- HUS:

- Caused by E. Coli O157:H7 bacterial infection
- Food borne
- Bacteria secretes toxin that activates complement system and causes endothelial damage, mainly in kidneys

HUS differs from DIC that in this disease there is no sepsis, there is a certain toxin that activates the complement system, so we there will be thrombosis by platelets, but not in the clotting factor pathway

Before we proceed, let's talk about VON WILLIBRAND FACTOR (vWF):

- Endothelial cells are normally the major source of vWF (it is normally found in the subendothelial area, so when there is a damage, it becomes exposed and it binds platelets to form platelets plug)
- It is also present in platelets granules and subendothelial area
- Facilitate platelets adhesion to damaged blood vessels
- It also stabilizes factor VIII (there are free circulatory vWFs, which carry factor VIII , so it is important to stabilize factor VIII , and if we have severe absence of vWF , this will affect the amount of factor VIII)
- Precursor of vWF is a large multimer molecule (remember TTP)
- Examined by ristocetin aggregation test(aggregation of platelets by ristocetin) (ristocetin enhances vWF binding to platelets), if no aggregation → vWF deficiency , and there is aggregation → vWF is present and active (this test is for the presence and activity of vwf)

4- VON WILLIBRAND DISEASE:

- Autosomal dominant
- Most common inherited bleeding disorder (1% of population in US) (very common)

▪ Affects platelets function (dominant symptom) and coagulation (factor VIII)
▪ Patients present with ecchymosis (and petechiae), easy bleeding and menorrhagia (menorrhagia in girls when they develop the period)
▪ In homozygous disease (more severe than heterozygous), factor VIII deficiency becomes severe enough to resemble hemophilia A disease (and then there will be bleeding in the skin and body cavities) (most patients are heterozygous status(one chromosome or one gene is affected))
▪ Type 1: most common, modest reduction of vWF level
▪ Type 2A: the precursor of vWF is not synthesized, too
▪ Type 2B: the precursor of vWF is unstable with very short half-life, capable of binding to multiple platelets causing thrombocytopenia as well (the precursor is hyper active) , (patients have picture similar to TTP)

In this disease platelets count is normal but they cannot function, so there will be symptoms similar to thrombocytopenia .

5- HEMOPHILIA A:

▪ X-linked disease (inherited disease , affects boys more than the girls)
▪ Most common cause of inherited serious bleeding (more serious than vWF disease)
▪ patients are born with deficiency in factor VIII (prolonged PTT) (if we examined the PTT of the intrinsic pathway, it is prolonged , but the PT is normal)
▪ 70% have a family history (we ask about the older brothers or the maternal uncles), 30% appears as a new mutation
▪ Severe disease occurs when the level of factor VIII drops to 1% of normal level (marked deficiency of factor VIII) (spontaneous bleeding) (naturally we have a huge reserve of factor VIII , so there is no symptoms unless factor VIII level drops below 20% of the normal one , then there will be bleeding , but the severe and life threatening bleeding occurs when the level droops to 1% of the normal level)
▪ Mild deficiency (most patients) : bleeding occurs after trauma or surgery (in

boys, earliest surgery they have is circumcision, so this disease can appear at that time)

- In 10% of patients: normal level but abnormal function (functional deficiency , prolonged PTT)
- Bleeding occurs in body cavities (joints, abdomen, chest and heart), no petechiae (in joints, there will be recurrent bleeding which cause damage to the joint and then abnormal joint > can't grow normally) (clotting factors deficiency like factor VIII , bleeding tends to occur in body cavities , deep in the tissue , not like the platelets deficiency that makes ecchymosis)
- Hemophilia B (rare) : identical to hemophilia A, less common, factor IX deficiency (different protein type)

6- THROMBOCYTOPENIA with 2 related diseases:

A) IMMUNE THROMBOCYTOPENIC PURPURA

B) HEPARIN-INDUCED THROMBOCYTOPENIA

THROMBOCYTOPENIA:

- Defined as platelets count below 150,000 cell/uL (once this occurs, it is not a must to have bleeding tendency and symptoms, this occurs when the count drops below 50000 , and spontaneous bleeding when the count drops below 5000)
- Increased risk of bleeding occurs when count drops below 50,000
- Spontaneous bleeding: <5,000
- Bleeding occurs in superficial parts of body (skin, mucous membranes), called petechiae and ecchymosis (platelets related bleeding)
- Larger hemorrhage occurs in brain (when there is marked thrombocytopenia) (usually body cavities are preserved)

the causes (similar to those in anemia) :

- Thrombocytopenia may occur in the setting of increased platelets destruction (bone marrow shows increased megakaryocytic activity) or decreased production from bone marrow

▪ HIV infection causes thrombocytopenia (both increased destruction and decreased megakaryocytic survival) (makes mixed picture, peripheral destruction increased and it also affects the megakaryocytes which causes decreased survival and thus decreased production)

A) IMMUNE THROMBOCYTOPENIC PURPURA :

(most important disease in platelets deficiency , autoimmune disease so it makes an isolated thrombocytopenia) (purpura, so there will be bleeding in the skin that is palpable (pinpoint) , so I have tendency to bleed in the skin as a result of thrombocytopenia)

▪ Acute ITP is seen in children after viral infection (self-limited) (there will be sensitization of platelets in an abnormal way and then consumption by the spleen)
▪ Chronic ITP is commonly seen in middle-age women (autoimmune disease so it needs specific therapy)
▪ Formation of autoantibody (IgG) against glycoprotein IIb/IIIa or Ib/IX complexes (in both acute and chronic) (detected in 80% of patients)
▪ Splenic histiocytes (or macrophages) remove coated platelets and destroy them (after the binding between the auto antibody and the glycoprotein , when the platelets reach the spleen)
▪ Splenomegaly is NOT prominent (like in hemolytic anemia) , but patients benefit from splenectomy (patients benefit from splenectomy so there will be no destruction of platelets and the thrombocytopenia is corrected)
▪ if we examine the bone marrow, it shows proliferating megakaryocytes (they are not absent or abnormal (like in MDS which makes thrombocytopenia but the megakaryocytes are abnormal) , they are proliferating like proliferation of normoblasts in hemolytic anemia)

B) HEPARIN-INDUCED THROMBOCYTOPENIA (HIT) :

(action of heparin is on the coagulation system (not on platelets) , unless it develops this complication)

▪ patients have moderate to severe thrombocytopenia affects 5% of patients receiving heparin after 1-2 weeks of therapy (after 1-2 weeks of taking heparin)
▪ in this disease there will be formation of IgG antibody that binds factor-4 (on platelets surface) in a heparin-dependent manner, resulting in platelets activation and thrombosis (consumptive thrombocytopenia) (platelets activation results in the formation of platelets plug within the blood stream , so there will be thrombocytopenia along with thrombosis (similar to paroxysmal nocturnal hemoglobinuria))
▪ Mostly seen in high-molecular weight heparin (in pharmacology we have two forms of heparin :
1- high – molecular weight which is commonly used , and this form makes this side effect
2- low – molecular weight (fractionated heparin , we take only the active subunit) and this form still can make this disease but much less common than the high molecular weight heparin (improved quality form of heparin))

THE END

يا غاصب شعبي لن يركع ...

NOTES AND CORRECTIONS

V.2 : page 9 > intrinsic pathway not extrinsic (the correction marked with yellow)