Common pediatric hematological diseases

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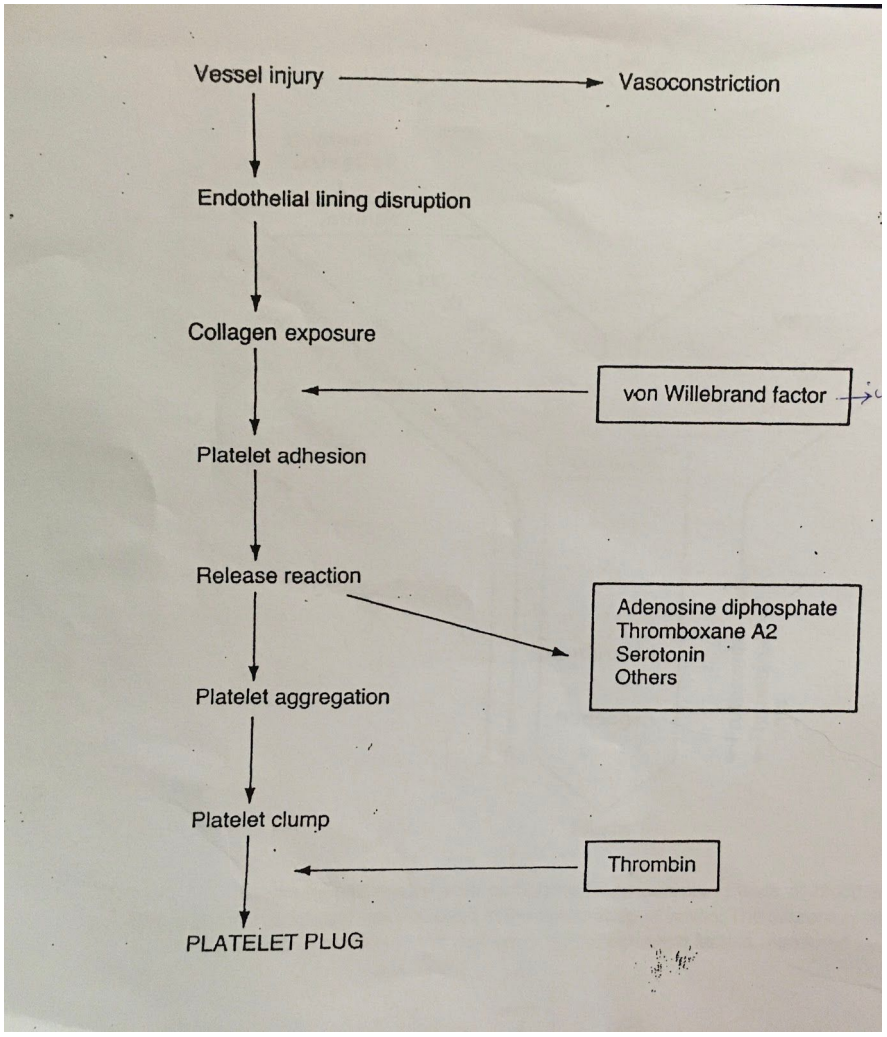
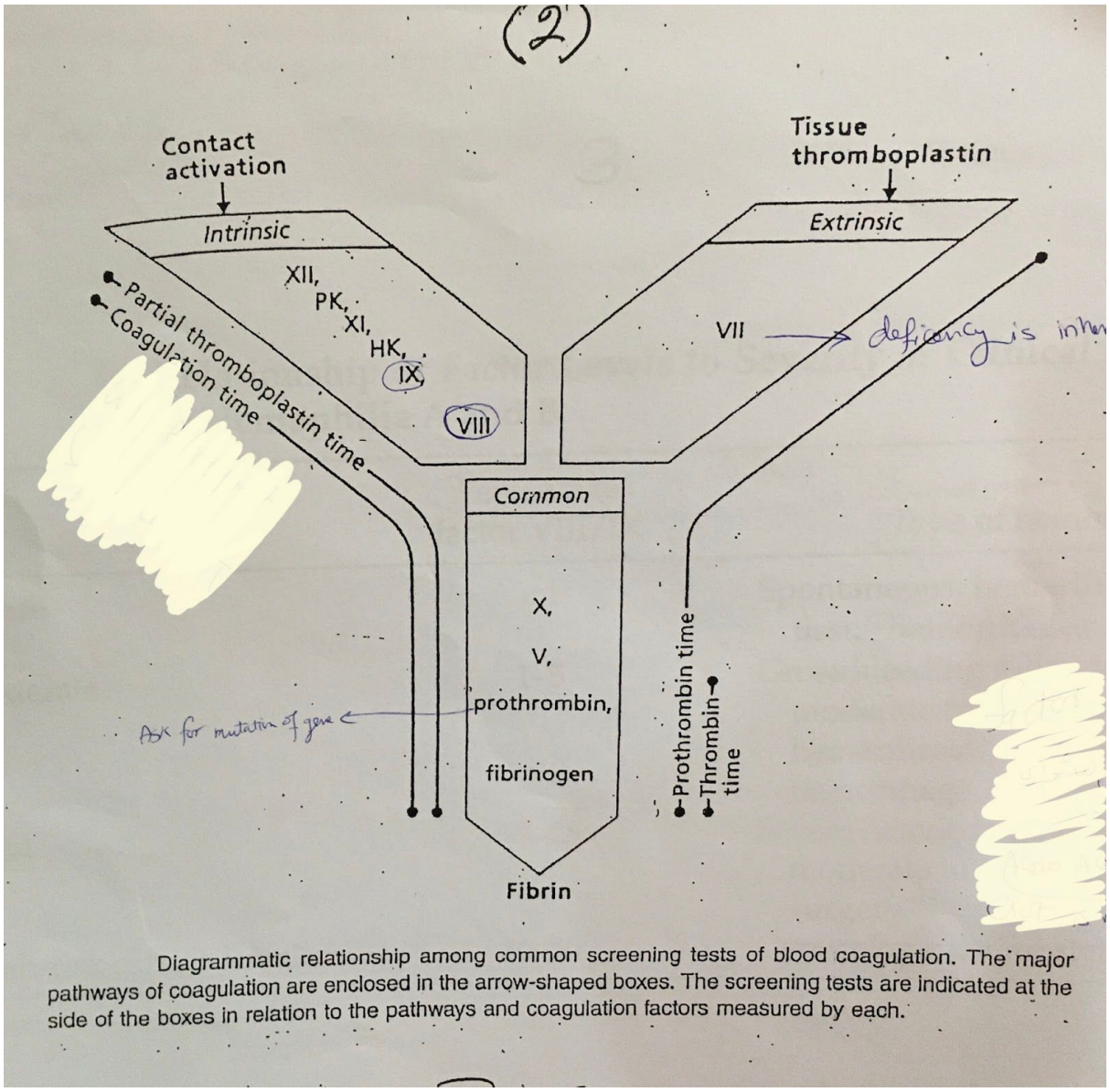
* No Slides. Only hard copy papers will be provided here.
* Notes

1- Primary Hemostasis (formation of platelet plug)



* If vWF is defective → Adhesion won't happen, therefore aggregation won't happen.

2- Secondary Hemostasis (Coagulation cascade)



Diagrammatic relationship among common screening tests of blood coagulation. The major pathways of coagulation are enclosed in the arrow-shaped boxes. The screening tests are indicated at the side of the boxes in relation to the pathways and coagulation factors measured by each.

* VII deficiency is inherited
*Lupus anticoagulant gives you high pTT.
To measure intrinsic pathway use: pTT, coagulation time.
To measure extrinsic pathway use: pT, thrombin time.
*Factor 13 (XIII) can't be measured by these tests, therefore we use a weak acid (e.g. Acetoacetic acid), in case of XIII defect, the clot will be resolved even by the weakest acid in the earth :) .

3- Relationship of factor levels to severity of clinical manifestations of Hemophilia A and B:

Type	Percentage (of function) factor VIII/IX*	Type of hemorrhage
Sever	< 1	Spontaneous; hemarthrosis and deep tissue hemorrhages.
Moderate	1-5	Gross bleeding following mild to moderate trauma; some hemarthrosis; seldom spontaneous hemorrhage.
Mild	5-25	Severe hemorrhage only following moderate to severe trauma or surgery.
High risk carrier females	30-50	Gynecologic and obstetric hemorrhage

*Hemophilic patients have normal number of factor VIII/IX, they only have a defect in their function.
*if you have a girl had hemophilia and her father only had hemophilia, what could explain it?
→ Lyonization of one gene in fetal life (X-inactivation) "extreme Lyonization".
*Brain hemorrhage is the worst presentation.

4- Differences between von Willebrand Disease and Hemophilia A:

	von Willebrand Disease	Hemophilia A
Symptoms	Bruising & epistaxis Menorrhagia or mucosal bleeding	Joint bleeding Muscle bleeding
Sexual distribution	M = F	Males
Frequency	1:200 ro 1:500	1:6000 males
Abnormal protein	vWF	factor VIII
-molecular weight	0.6-20 * 10^6 Da	280 KDa
-function	Platelet adhesion	Clotting cofactor
-site of synthesis	Endothelial cell or megakaryocyte	??
-chromosome	chromosome 12	X chromosome
Inhibitory freq	Rare	14-25% of patients
History	Abnormal	Abnormal
aPTT	Normal or prolonged	Prolong
factor VIII activity	Borderline or decreased	Decreased or absent
vWF Ag	decreased or absent	Normal or increased

*If Bleeding time is increased = vWF disease. | Normal Bleeding time in hemophilia.

*in Pedia, do PLT function instead of bleeding time.

*in hemophilia → normal Number of VIII, while in vWF disease → low VIII number.

*vWF disease is more common than hemophilia A/B.

*Type I vWF disease is the commonest.

5- Testing for Thrombotic Predisposition:

Hereditary predisposition to thrombosis is associated with a reduction of anticoagulant function (protein C, protein S, AT-III); the presence of a factor V molecule that is resistant to inactivation by protein C (factor V Leiden); elevated levels of procoagulants (a mutation of the prothrombin gene); or a deficiency of fibrinolysis (plasminogen deficiency). When patients are being screened for prothrombotic tendencies, specific tests of the natural anticoagulants are warranted. Although both immunologic and functional tests are usually available, functional assays of protein C, protein S, and AT-III are clinically more useful.

Factor V Leiden is a common mutation in factor V that is associated with an increased risk of thrombosis. A point mutation in the factor V molecular prevents the inactivation of factor Va by activated protein C and, thereby, the persistence of factor Va. This defect, also known as activated protein C resistance, is easily diagnosed with DNA testing.

The prothrombin gene mutation (G20210A) is a mutation in the noncoding portion of the prothrombin gene, with a (G) at position 20210 being replaced by alanine (A), that mutation increases the amount of prothrombin messenger RNA, is associated with elevation of prothrombin, and causes a predisposition to thrombosis. This abnormality is easily identified with molecular diagnostic DNA testing.

6- Elevated Homocysteine:

Levels of homocysteine may be increased as a result of genetic mutations, causing homocystinuria. patients with homocysteine elevation are predisposed to arterial and venous thrombosis as well as to an increased in arteriosclerosis.

7- Potential prothrombotic states:

Congenital
Deficiency of anticoagulants AT-III, protein C or protein S, plasminogen Resistance to cofactor proteolysis Factor V Leiden High levels of procoagulants Prothrombin 20210 mutation Elevated factor VIII levels Damage to endothelium Homocystinuria
Acquired
Obstruction to flow Indwelling lines Pregnancy Polycythemia Immobilization Injury Trauma, surgery, exercise Inflammation IBD, vasculitis, infection, Behcet syndrome Hypercoagulability Pregnancy, malignancy, antiphospholipid syndrome, nephrotic syndrome, oral contraceptives, L-Asparaginase, elevated factor VIII levels.
Rare other entities
Congenital Dysfibrinogemeia Acquired Paroxysmal nocturnal hemoglobinuria Thrombocythemia Vascular grafts

*__Factor V Leiden__ is the commonest cause of thrombosis.

It is inherited, autosomal dominant.

Factor V is normally inactive by the action of protein C. but in this disease, because its structure is altered, protein C wont recognize it, therefore, it will remain active → thrombosis.

8- Immune Thrombotic Purpura (ITP):

- 90-99% of platelet disorders is ITP.
- It is a state of low PLT.
- Remember, the 1st thing to be consumed in a sick child is PLT (may go through DIC)
- Acute ITP → < 1 year | Chronic → > 1 year. | Brain hemorrhage occur within the 1st month of ITP.
- Start by **History**.
    - When it happens?
    - The commonest cause of ITP is viral infection (within 3 weeks back)
    - Drugs → may generate IgG or antibodies other than IgG.
    - Review of systems is important. (e.g. autoimmune disease manifestation)
    - Family history → for autoimmune.
- **Physical exam**: you should do your best! esp in liver and spleen exam.
    - If spleen is palpable → this is leukemia not ITP!!
- **Investigations**:
    - CBC → all should be normal except PLT, even though Hgb it should be normal, not in borderline!
        - Admit → if PLT <20,000 . / If PLT >40,000 → go home, come back after 1 week.
    - T4, TSH → looking for thyroiditis (it may cause low PLT)
    - ANA, C3, C4 → autoimmune.
- **Management:**
    - PLT transfusion is contraindicated !!
    - Give immunoglobulins with (before administering IgGs, give hydrocortisone or panadol, … | why? to prevent meningismus "therefore brain hemorrhage" triggered by IgG → small molecules may cross BBB).
    - **Drug of choice for ITP → Prednisolone (MCQ)** (give for 2-3 weeks) بالرغم من أنه أفضل واحد, إلا إني ما أعطيه أول شيء لأنه ياخذ له أيام على ما يشتغل وأنا أخاف المريض ينزف في دماغه وتوه ما اشتغل العلاج, لذلك أبدأ الخطة العلاجية حقتي (بالأجسام المضادة إميونوقلوبيلنز لأنها سريعة
    - للفقراء اللي ما يقدرون على سعر الimmunoglobulins أعطيهم بداله Anti D Ig .. جيد لكنه ممكن يسوي hemolytic anemia.
    - **What if all treatment fail**?

- Go for Rituximab! drug of choice if all Tx not worked! how does it work? most of immunoglobulins given are IgG1, Rituximab work on prolong IgG1 life. (only 30% of pts will respond to Rituximab)