Lec 8: Thalassemia

- It is the most common genetic disorder on worldwide basis.
- It is an inherited blood disorder effect on body ability to produce normal hemoglobin and healthy red blood cells, types include alpha and beta thalassemia.
- Thalassemia may cause anemia-like symptoms that range from mild to severe. Treatment can consist of blood transfusions and iron chelation therapy
- Children with thalassemia have shorter RBC life, more HbF, & the RBCS are more sensitive to the oxidative stress**.**

Pathophysiology

- In β-thalassemia, there is an excess of the α-globin chains relative to the β-globin chains & γ-globin chains, which → α-globin tetrameric inclusions (α4) which interact with RBC membrane & ↓ RBC survival → anemia & ↑ erythroid production. There are normal levels of γ-globin & δ-globin chains production, which → ↑ HbF (α2γ2) & ↑ HbA2 (α2δ2) respectively.
- In α-thalassemia, there is an excess of the β-globin & γ-globin chains relative to α-globin chains, which → Bart's Hb (γ4) in fetal life & HbH (β4) after birth, which → extravascular hemolysis.
- In bone marrow, the thalassemic mutations disrupt the maturation of the RBCS, which → "ineffective erythropoiesis" i.e. the marrow is hyperactive but there are relatively few reticulocytes associated with severe anemia.

Thalassemia causes:

- Hemoglobin consists of four protein chains, two alpha globin chains and two beta globin chains
- Alpha globin protein chains consist of four genes, two from each parent.
- Beta globin protein chains consist of two genes, one from each parent
- Any defective or missing in genes coding for globin chains in hemoglobin are caused thalassemia.
- The extent of the defect will determine disease severity

Types of thalassemia:

- There are two types of thalassemia — alpha and beta thalassemia — named after defects in these chains.
- Each type of thalassemia is classified as minor and major.
- Thalassemia major is the most serious form and usually requires regular treatment,
- Thalassemia minor means that you may experience mild anemia symptoms or no symptoms at all. You may not need treatment.

Alpha thalassemia types include

A. One deletion: Silent carrier
B. Two deletion: Minor alfa thalassemia
C. Three deletion : HbH disease
D. Four genes deletion: Bart's hydrops fetalis syndrome

HbH disease :The absence of 3 a-chains affect called, started in fetus life and survive to adult life with (symptoms)

1. Severe anemia with hemolysis.
2. Occasionally blood transfusions are required
3. Severe RBC abnormalities
4. The absent of 3 alpha chains make Precipitated Hgb H inside the RBC
5. HbH disease diagnosed early at about 6 months.

Laboratory diagnosis of HbH Thalassemia:

1. CBC: Low Hb , low MCV , normal RDW, increased retic count
2. Blood Film: hypochromia , microcytosis , target cells , basophilic stippling and tear drops
3. Hb Electrophoresis: Hb A (absent) , HbA2 (normal) , HbF(slightly elevated) , HbH (90%)
4. DNA analysis searching for the alpha genes on the chromosome 16 (three are absent)
5. Red cell inclusion bodies in reticulocyte preparations (may be reach to 70% of all RBC) by supravital stain, increasing incubation time to cause precipitation giving the appearance of a golf ball

Bart's hydrops syndrome: occurs when no chains are made (deletion 4 chains), even in the fetus; these infants are usually stillborn at between 28 and 40 weeks, and if born alive, they die within the first hour.

Beta Thalassemia types include

- Minor type _when mutation caused deletion of one beta chain,
- Major β –Thalassemia called (Cooley's Anemia) that defect in both beta chains (the towbeta chains are absent).

Symptoms of Major β –Thalassemia (Cooley's Anemia):

1- Severe anemia at 6 months of birth.

2- HbF not developed to HbA in the first year of the life

3- The result remain the HbF all life with sever hemolysis

4-Most patients need regular transfusion.

5-The main problem of those patients is iron loading.

Laboratory diagnosis of Cooley's Anemia:

1. **CBC:** Low Hb, Low MCV, RDW , increased retic count
2. **Blood Film:** Hypochromia , microcytosis , target cells , basophilic stippling and tear drops , NRBC , and Heinz bodies
3. **Hb Electrophoresis:** Hb A (absent) , HbA2 (normal) , HbF about 90%
4. **DNA analysis:** For the β genes on the chromosome 11 (three are absence of two beta chains).

Minor β –Thalassemia: Deletion of one beta chain that characteristic by:

1-RBC is elevated over 5.5 million per mm^3.

2-Not needs blood transfusion.

3-No hemolysis.

Laboratory diagnosis of Minor β-thalassemia:

1. **CBC:** high RBC count , low HB, MCV, normal RDW, slightly increased retic count
2. **BF:** Hypochromia , microcytosis, target cells , basophilic stippling
3. **HB electrophoresis:** Hb A (over 60%) , HbA2 (4-7%) , HbF (normal)