THALASSEMIA:

A thalassemia is a group of inherited disorder caused by deficient globin chain synthesis due to mutation in Globin genes.

- ↓ or Absence of synthesis of either α or β Globin chain.

Normal Hb : 4 Globin chain { 2α, 2 non α } chain

① HbA : 2α, 2β ② HbA_2 - 2α, 2δ ($\alpha_2\delta_2$)

③ Hbf : 2α, 2γ ($\alpha_2\gamma_2$)

CLASSIFICATIONS:

- β thalassemia : Due to unpaired synthesis of β chains
- α Thalassemia : Unpaired synthesis of α chains.
- Miscellaneous thalassemic syndromes.

- The basic defect is usually a quantitative Abnormality with Reduced or Absent production of the Resp globin chains.

- The lack of one globin chain leads to unpaired normal globin chain in RBCs., In β thalassemic excess normal α chains form unstable structure that precipitate at the RBC membrane

β Thalassemia:

- Autosomal Recessive disorder.
- ↓ syn of β globin chain of normal synthesis of α chains
- Point mutation leading to Abnormal RNA splicing are the most common cause.
  - ↪ β^0 : no production of β chains
  - β^+ - Reduced syn.

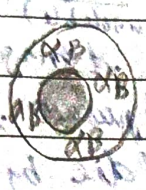
→ Mediterranean fever

B thalassemia Major: Mediterranean / Cooley's Anemia

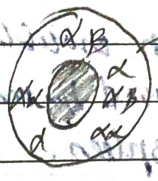
→ syn of β globin chain affected but not α chain.

– genotype: homozygous form of β^0/β^0 or β^+/β^+ or β^0/β^+

PATHOGENESIS:



Reduced β globin synthesis
excess of α globin



→ excess of α globin
[insoluble]

Normal RBC

Abnormal normoblo

↓ Reduced production

α globin Aggregate HbA

[Ineffective erythropoiesis]

Microcytic hypochromic RBC

Extravascular hemolysis

Anemia

Tissue hypoxia

Erythropoietin

Enlarged Hyperplasia

Bone expansion

(skeletal deformities)

[Iron overload]

Liver

Heart

systemic iron overload

(secondary hemochromatosis)

→ defective syn of β globin cause Anemia by 2 Mechanism:

① Inadequate HbA formation: ↓ syn of β chain

↓

↓ HbA formation.

RBC are poorly Hb inked (Hypochromic Microcytic)

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② Accumulation of unpaired α chain:

→ They form toxic products damage the membrane Red cell of erythroid precursors.

Extravascular Hemolysis:

- RBC with trapped α are removed by macrophages of spleen.

Ineffective erythropoiesis (extramedullary)

- α globin damage membrane of erythroid precursor, they fail to mature & die by Apoptosis in BM
- Marked erythroid hyperplasia
- skeletal deformities:

→ Skull X Ray - Hair on end appearance.

↓

due to new bone formation.

The diploic layer widen due to marked erythropoiesis.

→ Typical facies: chipmunk face - prominent forehead, cheekbones, upper jaw.

Iron overload:

→ Ineffective hematopoiesis produces → erythroferrone which suppresses the Hepcidin

↓ Hepcidin leads to ↑ Absorption of Fe

↓

Fe overload

↓

Hemosiderosis

In β thalassemia γ chain are synthesized even after birth which combine with α → ↑ HbF ($\alpha_2\gamma_2$)

Cause - Growth Retardation (cachexia)

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CLINICAL FEATURES:

→ Age : Infant develop Anemic 6-9 After birth.
→ Untreated children fail to thrive, die with 4-5 years of Age
→ Bone changes → deformities of skull, facial Bone,
hair on end appearance
- chipmunk face.
→ splenomegaly.
- Extramedullary hemopoiesis
- Iron overload - hemochromatosis.

Lab findings: ↓Hb, RBC count ↓, Reticulocyte ↑, MCV ↓, MCH ↓ MCHC ↓

Peripheral smear:
→ Hypochromic Anemia
- Anisocytosis & poikilocytosis.
- Target cells: They have ↑ surface area to volume Ratio, Not Allow Cytoplasm to collect in central dark Red puddle
In such way that only the periphery of central Region of RBC appears hemoglobinized.
- Basophilic stippling.
- Nucleated RBC.
→ WBC → leukocytosis
→ Platelets → Normal ↑
B.M → hypercellular
M:E Ratio → Reversed to 1:1 to 1:5.
Iron ↑ due to dietary Abnormal
Normoblastic with Marked erythroid hyperplasia.

Biochemical: ↑ Bilirubin
↑ urine urobilinogen.
↑ serum Iron
↑ TIBC ↓

Rx
→ ↑ HbF
→ Hb electrophoresis
→ High performance liquid chromatography

NON - HODGKIN'S