Thalassaemias

Definition:

Family of inherited haemoglobinopathies resulting from decreased synthesis of α or β globin chains.

Clinically they r divided into :

1-Thalassamia major: (Transfusion dependent)

A- Hydrops foetalis

B- β Thalas. Major

2-Thalassamia intermedia:

Ch. by moderate an. usually e' splenomegaly & iron overload.

3-Thalassamia minor: symptomless carrier.

β Thalassamia

Def:

Severe H.A in infancy & early childhood e' certain characteristic features:

- MHA
- Anisocytosis, poikilocytosis, target cs.
- Splenomegaly
- Mongoloid facies
- serum iron
- Patient usually dies from cardiac arrhythmias

Clinical classification:

Thalassamia major

,, intermedia

,, minor

Genetic classification:

β = normal gene

β+ = partial synthesis of β chain

β o = complete absence of β chain

Genetic expression may be:

1-βoβo : thalas. Major

Hb: all r F & A2 (no Hb A)

2- β+β+ : thalas. major or intermedia

variable amount of Hb A, F & A2

3-β+βo : thalas. major or intermedia

variable amount of Hb A, F & A2

4-ββo : thalas. minor or intermedia

Hb A, F & ↑ Hb A2

5-ββ+: thalas. minor or intermedia

just ↑ Hb A2

Classification & Terminology of Beta Thalassemia

- Normal β/β
- Minor β/β^0
  β/β^+
- Intermedia β^0/β^+
  β^+/β^+
- Major β^0/β^0
  β^+/β^+
  β^0/β^+

Molecular basis of β thalassamia

The defect mainly is Quantitative : due to amount of m-RNA.

Most of β thal. syndromes r caused by mutations affecting gene regulation or expression rather than gene deletion (unlike α thalas.)

N.B: causes:

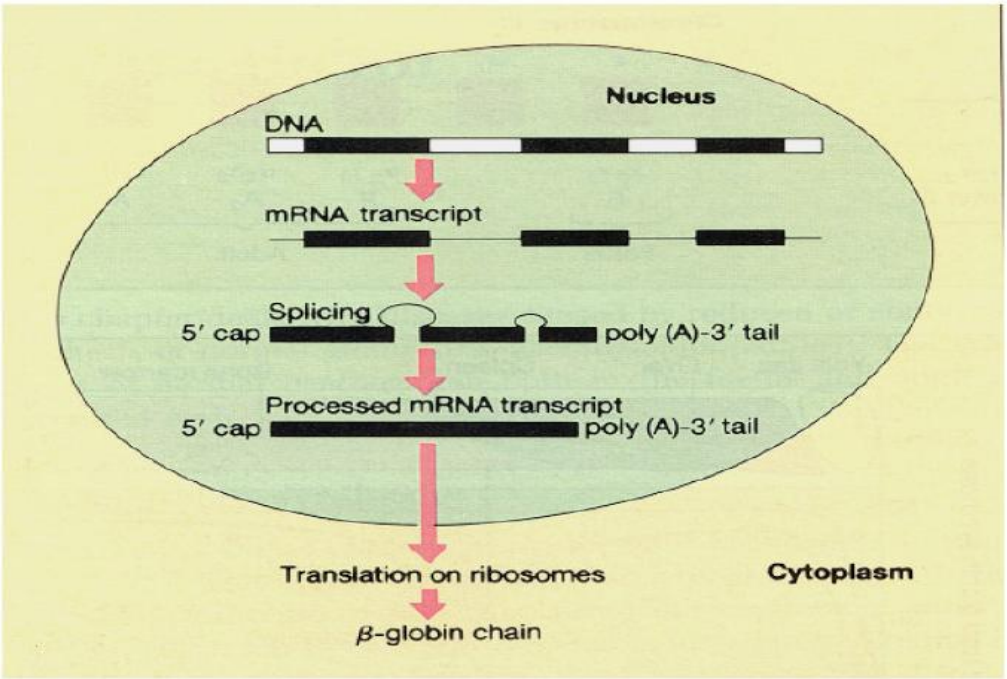
1- Deletion:

2- Non deletion:

A- mutation of m-RNA transcription

B- ,, ,, processing

C- ,, ,, translation



I- Deletion: βo Rare

Deletion of a part or whole of 3' or 5' end of β gene (mainly in α thalassamia not β).

II- Non deletion = Mutation:

A- Mutations of transcription:

1-promotor region mutation: β+

↓ m RNA transcription → ↓amount of globin synthesis → ↓synthesis of β chain = β+

2- chain terminator mutation: βo

This leads to : mRNA is incapable of being translated into full length globin chains resulting in βo phenotype.

B- Mutations of processing:

Mutations affecting splicing, capping or polyadenylation → unstable m-RNA → ↓amount of globin synthesis → ↓synthesis of β chain

1- Splice junction mutations : βo

- Point mutation involving splicing sites result in abnormal splicing.
- The m-RNA produced is useless as a messenger for β globin synthesis → βo

2- Mutations of consensus sequences : β+

- Mutations involving consensus seq. (boundaries surrounding splice junction) results in formation of cryptic donor site.
- These cryptic sites resemble N splice sites but r not recognized unless N sites r altered.
- These mutations leads to ↓splicing not abolish it → β+

3-Mutations creating new splicing sites: β+ or βo

- Nucleotide substitution e'in introns results in formation of new splice sites, despite of presence of functioning N splice sites.
- The new splice sites compete e' N splice site → β+ or βo

4- Activation of cryptic donor site : β+

- Exons contain cryptic sites e' a nucleotide sequence resembling N seq.
- Mutations of these cryptic sites lead to their activation, competition between abnormal new splice seq. & N splice seq → mild β+

5-Mutations of polyadenylation : β+

Mutation of AATAAA seq. at 3' end → transcription continue elongated m-RNA (unstable) → β+

6- Mutations at cap site : β+

Substitution of C for A in 1st position may ↓ transcription or slow the 5' capping → ↓ m-RNA stability → β+

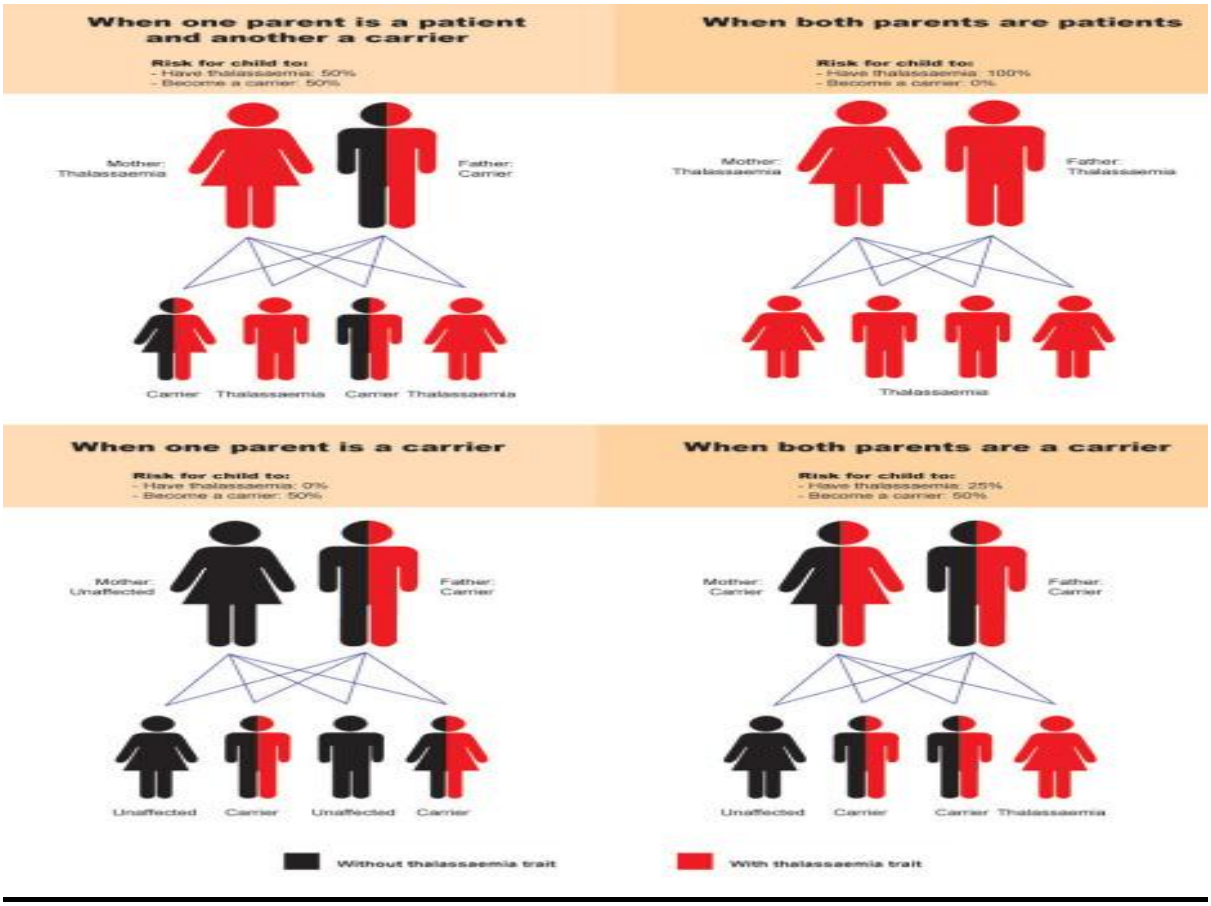
C- Mutations causing abnormal translation of m-RNA:

1- Nonsense mutation : βo

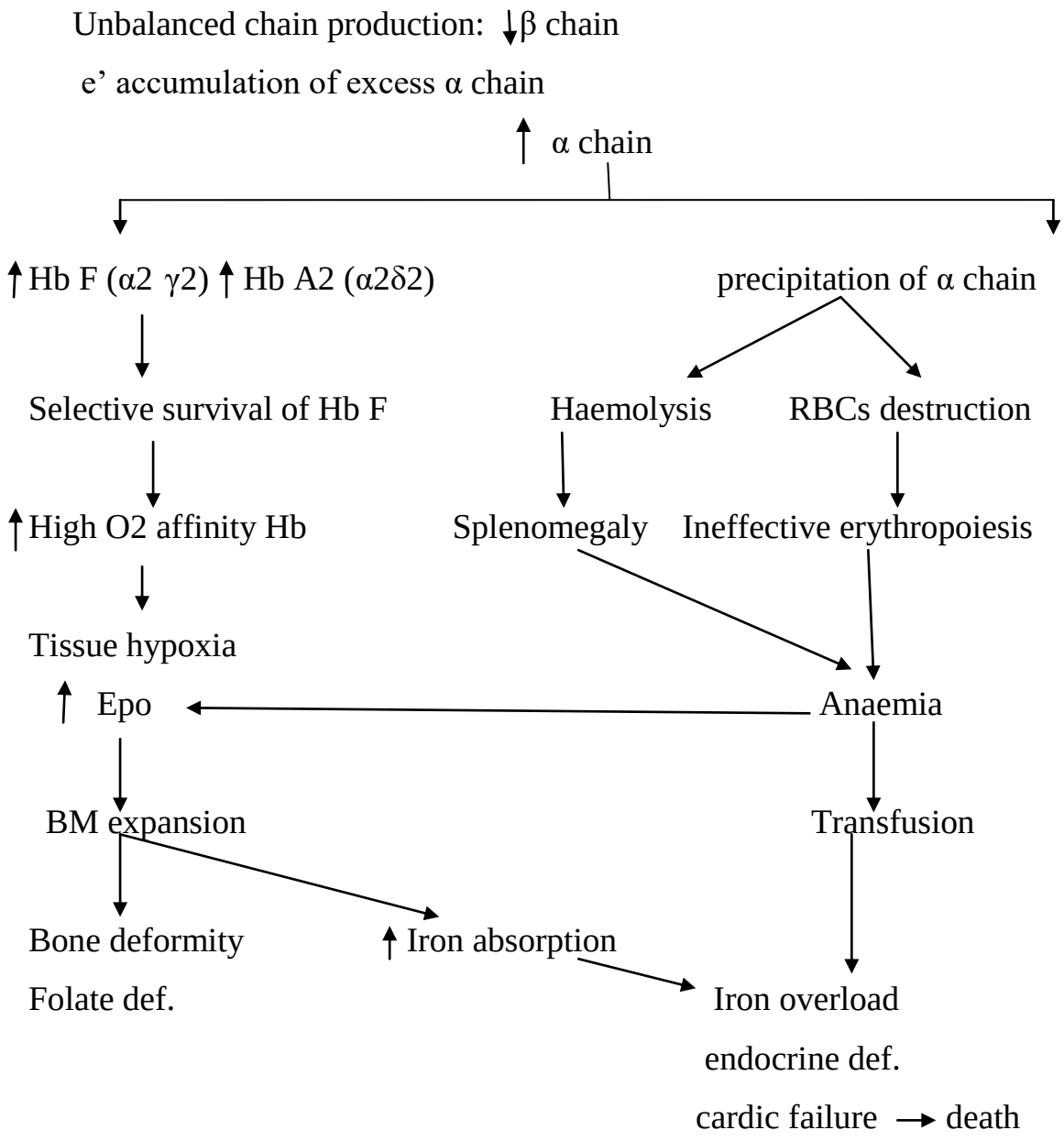
Point mutation (single aa substitution) creation of a stop codon → prevent translation of m-RNA → premature stop codon → βo

2- Frame shift mutation:

1,2,4 base insertion or deletion → disturbance of N reading frame → creation of termination codon


When one parent is a patient and another a carrier
Risk for child to:
- Have thalassaemia: 50%
- Become a carrier: 50%
Mother: Thalassaemia
Father: Carrier
Carrier
Thalassaemia
Carrier
Thalassaemia
When both parents are patients
Risk for child to:
- Have thalassaemia: 100%
- Become a carrier: 0%
Mother: Thalassaemia
Father: Thalassaemia
Thalassaemia
When one parent is a carrier
Risk for child to:
- Have thalassaemia: 0%
- Become a carrier: 50%
Mother: Unaffected
Father: Carrier
Unaffected
Carrier
Unaffected
Carrier
When both parents are a carrier
Risk for child to:
- Have thalassaemia: 25%
- Become a carrier: 50%
Mother: Carrier
Father: Carrier
Unaffected
Carrier
Carrier
Thalassaemia
Without thalassaemia trait
With thalassaemia trait

Pathophysiology



Thalassamia major (Cooley's anaemia)

Severe anaemia manifested early in life e' splenomegaly & bony deformaties

Genetic expression:

βo/βo

β+/β+

βo/β+

δβ lepore / δβ lepore

βo/E → (Hb E → thalassamic Hb as it is abnormal Hb & ↓ amount

C/P:

of chronic H.A

Lab findings:

1- Evidences : 3

2-CBC:

- MHA
- Target cells, macrocytes (↑retics)
- Anisocytosis, poikilocytosis
- ↑Normos
- basophilic stippling, capot rings
- retics ↑but doesn't correlate e' degree of anemia (ineff.eryth)
- WBCs & platelets: N

3-BM:

Hypercellular, erythroid hyperplasia

Iron stain:

↑ iron stores, ↑ sideroblasts.

4- Evidence of ineffective erythropoiesis

5-Special tests:

A- Hb electrophoresis:

↑ Hb F & A2

Hb A (variable acc. to genetic variant & molecular basis)

B- Osmotic fragility:

↓ due to ↑ retics w' resist lysis

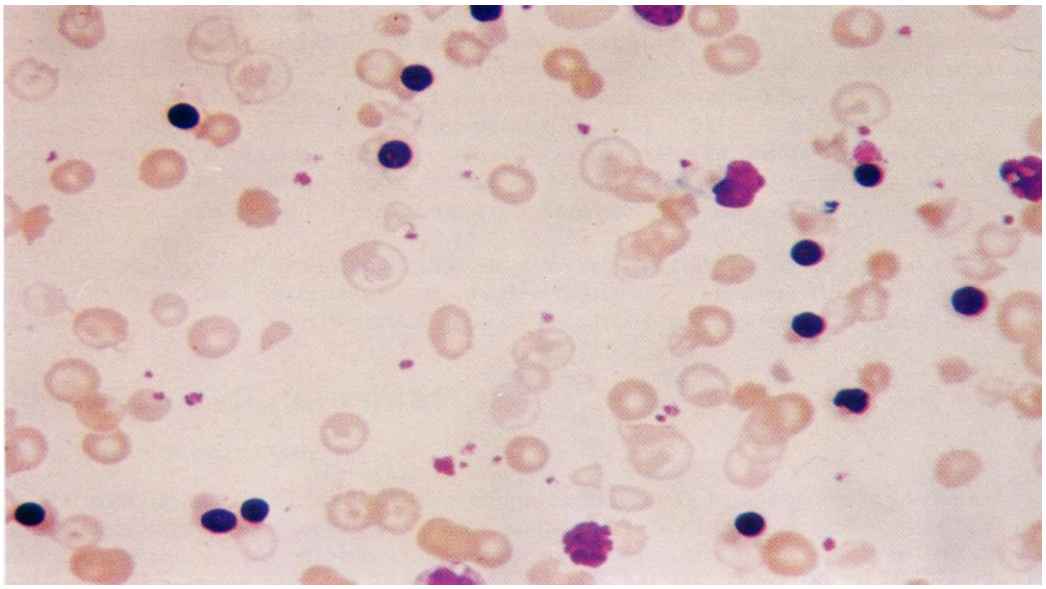
C- Ferrokinetics:

Ineffective erythropoiesis

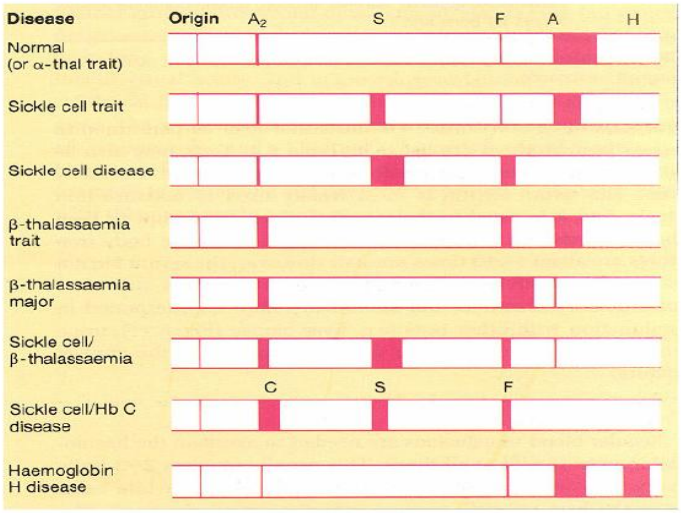
D- Gene study by PCR:

For prenatal diagnosis.

Thalassemia major



HB ELECTROPHORESIS



Thalassemia Intermedia

Milder than thal. major but more severe than asymptomatic thal. Trait

Genetic expression:

β+/β+

β/βo

βo/(δβ)o

β+/(δβ)o

(δβ)o/(δβ)o

double heterozygous lepore:

β+/ δβ lepore

βo/ δβ lepore

Coinheritance of α thalas. (↓α chain)

Hb H (αo/α+)

C/P:

Varies from:

1- severe:

- Patient presents e' anaemia later than thal. Major
- Hb 6 g/dl e'out transfusion
- Growth retardation
- Skeletal deformaties
- Splenomegaly
- Leg ulcers

2- completely asymptomatic until adult life & transfusion independent e' Hb level 10-12 g/dl

3- varieties of intermediate severity

Lab diagnosis:

- same as thal.minor
- Hb A : 20-40%

Thalassaemia minor

Pathogenesis:

↓ β or ↓ δβ synthesis

Genetic expression:

β/β+

β/βo

β/(δβ)o

β/δβ lepore

Hereditary persistence of fetal Hb (HPFH)

αo thalas. trait

α_+ thalas. Trait

C/P:

Asymptomatic, discovered accidently

Lab :

- Anaemia is mild or absent, but ↓MCV, ↓MCH
- RBCs:
- Hypochromia, target cs, basophilic stippling
- WBCs & plat: N
- chemistry:
- ↑ iron or ↑ferritin
- Hb E/P:
- ↑ Hb A2 & F

D.D:

Iron def. an. (MHA)

	Thalassamia minor	**Iron def. anaemia**
Serum iron	↑	↓
Serum ferritin	↑	↓
Iron stores	↑	Absent
sideroblasts	↑	↓
Hb A2	↑	↓

Treatment for Beta Thalassemia

- **Trait –** no treatment required
- **Intermedia**
- **Major (Cooley anemia)**
    - **Regular folate supplementation**
    - **RBC transfusion** (Splenectomy may decrease need for transfusions)
        - to maintain [Hgb] ~9-10g/dL
        - Blood transfusions → iron accumulation → iron overload
        - Iron chelators (disferroxamin)
        - **Bone marrow transplantation (BMT)**

    -BMT has been attempted from donors with matching alleles.

    - **Gene therapy—the future**