Anemia is defined as a Reduction in Circulating RBC mass

→ presents with sign and symptoms of hypoxia (all due to ↓ O_2)

→ weakness, fatigue, dyspnea

→ pale conjunctiva & skin.

→ headache & lightheadedness

→ Angina - especially with pre-existing CAD.

→ RBC mass is difficult to measure. (there are ways but expensive)

↓ instead we use.

↓ Surrogate

Hb	hematocrit	RBC count

- Why surrogates? Why can't we say Red cell mass ≡ Hb, Hct, measure RBC count

↓

Cause these are all concentration dependent

Case 1

eg: In pregnancy → as blood volume ↑, it could get diluted so Hb ↓.

↓

But that doesn't means Red cell mass ↓

→ If gun shot wound. Case 2

↓

Since blood as whole is lost.

↓

Hb concentration remains same.

↓

but RBC cell mass ↓.

→ only when we get fluids back into system, can we appreciate Hb ↓.

Definition:

Hb < 13.5 g/dL in males.

Hb < 12.5 g/dL in females.

Based on MCV, anemia can be classified as.

- Microcytic (MCV < 80)
- Normocytic (MCV = 80–100)
- Macrocytic (MCV > 100)

MCV → estimate of size of red blood cells.

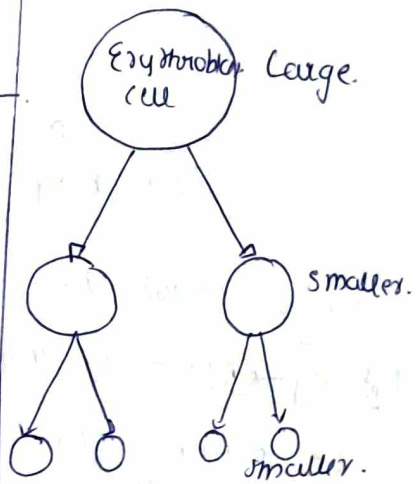
Classification based on MCV

↓

Best method.

MICROCYTIC Anemia.

- In microcytic anemia, RBC are small.
- MCV < 80



→ RBC's are formed from erythroblasts.

→ in each division, size ↓.

- In microcytic anemia, there is 1 extra division

→ This extra division is responsible for microcytes.

→ why do they do that extra division?

→ It is always due to ↓ production of Hb.

↓

RBC → in order to maintain Concentration normal.

↓

does 1 extra division become smaller → solid ✓

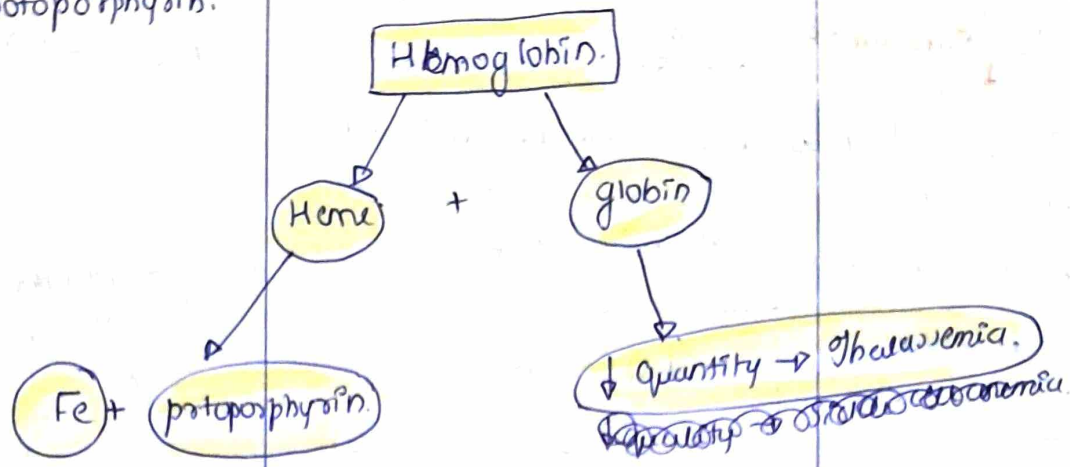
Microcytic Anemia

Gold

Hemoglobin

- Made of Heme & globin.
- What is heme?

Fe + protoporphyrin.



anemia could be due to

I ↓ Fe → ① iron deficiency

② → Anemia of chronic inflammation.

↓

iron is locked in macrophages

II ↓ protophorphyrin.

- sideroblastic anemia.

microcytic anemia

- Iron deficiency anemia.
- Anemia of chronic disease.
- sideroblastic anemia.
- Thalassemia.

Thalassemia

- There is decreased production of globin chain.
- So there is decreased production of Hemoglobin
- Leads to microcytic anemia

- due to inherited mutation.
- carriers are protected against plasmodium falciparum malaria.

Thalassemia

α β

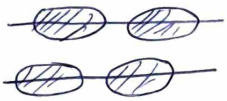
- If there is ↓ production of α globin chain → α thalassemia.
- If there is ↓ production of β globin chain → β thalassemia.
- Normal types of Hb
  - → HbF ($\alpha_2\gamma_2$)
  - → HbA ($\alpha_2\beta_2$)
  - → HbA$_2$ ($\alpha_2\delta_2$).

α is everywhere right? so we can remember that α has 2 genes with 4 alleles, cause it's more imp.

α - Thalassemia

Neo

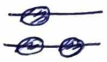
- Usually due to gene deletion
- Normally 4 α alleles are present on chromosome 16



4 alleles.

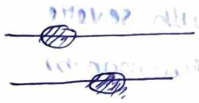
1 gene deleted

- Asymptomatic

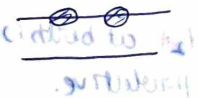


2 gene deleted

- mild anemia with slightly ↑ RBC count.



trans deletion. (common).

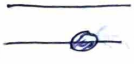


cis deletion (worse)

Cis deletion

- Associated with increased risk of severe thalassemia in offspring.
- Seen in Asians.

3 gene deleted.



- Severe anemia.
- Fetal life - $\alpha_2\gamma_2$ - no problem
- adult → β chain forms tetramer β_4

- β chains form tetramer (HbH) that damage RBCs.

$\beta_2 + \beta_2 \rightarrow \beta_4$

↓

HbH.

β_4 → HbH

- HbH is seen on electrophoresis

4 genes deleted

- lethal in utero (hydrops fetalis) dies in utero.
- γ chains form tetramers

γ_4 → Hb Barts that damage RBCs.

- Hb Barts is seen on electrophoresis

β - Thalassemia

two β genes are present on chromosome 11

- β thalassemia is due to gene mutation
- mutations result in absent (β^0) or diminished (β^+) production of β-globin chain.

Beta thalassemia minor

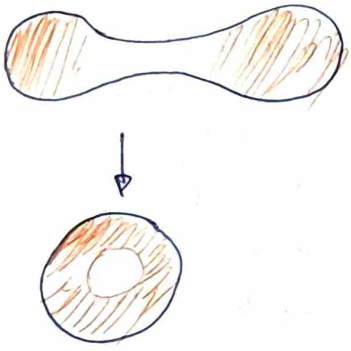
(β / β^+) → mildest form.

- Usually asymptomatic with ↑ RBC count.
- Microcytic hypochromic RBC and target cells on blood smear.

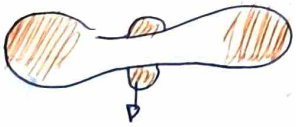
Combination)
(β, β^+)
(β, β^0)
(β^+, β^0)
(β^+, β^+)
(β^0, β^0)

Target cell.

Normal.



Target cell.



Bleb of membrane in centre.

↓

allow Hb in centre.

↓

TARGET CELL.

β-Thalassemia Major

(β^0 / β^0).

- most severe form.
- no problem in fetus. HbF ($\alpha_2\gamma_2$).
- presents with severe anemia, a few months after birth.
- HbF ($\alpha_2\gamma_2$) at birth is temporarily protective.

↓

there are no β chains.

↓

α tetramers aggregate and damage RBC.

- Ineffective erythropoiesis.
- Extravascular hemolysis (RE of spleen).

- Ineffective erythropoiesis ⇒ when RBC are made, & destroy them.
- Extravascular hemolysis

→ RE of spleen recognize & destroy abnormal RBC.

Since they have such severe anemia, they get

↓

Massive erythroid hyperplasia.

- Expansion of hematopoiesis into marrow of skull & facial bones.

↓

due to massive erythropoietin by kidney.

- Extramedullary hematopoiesis (liver, spleen)

↓

Hepatosplenomegaly

- Risk of aplastic crisis with parvovirus B19.

Thalassemia

- Crew cut appearance
- Chipmunk face

- Chronic transfusions are often necessary.
- Leads to risk for secondary hemochromatosis

Blood Smear.

- Microcytic, hypochromic. Target cells and nucleated red blood cells.

Nucleated red blood cells escape when hemopoiesis occurs in spleen, liver

- diagnosis — β thalassemia major
- diagnosis
- peripheral smear findings
- Bone marrow findings ?
- investigations for diagnosis.

- β thalassemia major, also termed Mediterranean or cooley's anemia.
- is the most common form of Congenital hemolytic anemia.
- homozygous state (β^0/β^0).
  - complete absence of synthesis.
- or only small amounts of β chain are formed (β^+/β^+)
- Quantitative disorder.

etiopathogenesis

etiology → Autosomal recessive.
→ β globin chain are encoded by single gene @ chr-11.
↓
mutations in β globin gene.
most common being point mutations leading to aberrant RNA splicing.
↓
homozygous form - β^0/β^0, β^+/β^+
or double heterozygous (β^+/β^0)
form ↓ β chain production.
↓
Hemolytic anemia of severe type

α-chain synthesis - unaffected.

pathogenesis

Severe hemolytic anemia occurs due to

① absence of β globin chain.
↓
absence of synthesis of HbA (α_2, β_2)
↓
formation of hypochromic microcytic anemia.

② Ineffective erythropoiesis

Unpaired & excess α-chains aggregate into insoluble precipitates.
↓
by themself
↓
damage membrane of erythroid precursors.
↓
fail to mature and undergo apoptosis in BM.

③ Extravascular hemolysis

RBC with α chain inclusions are removed by spleen.

Consequences of ineffective erythropoiesis

- erythroid hyperplasia.
- skull x-ray - hair on end / crew cut
- Typical facies → chipmunk.
  prominent forehead, malar bone, upper jaw.
- + Extramedullary hematopoiesis
  ↓
  hepatosplenomegaly.

- Iron overload and it's consequences

Causes of overload.

1. ↑ absorption of dietary iron
2. Hemolysis
3. Repeated transfusions.

Iron overload produces hemosiderosis and secondary hemochromatosis and damages to parenchyma of organs.

Clinical features (from figure)

- Age – infants develop moderate to severe anemia 6-9 months after birth. {HbF → HbA switch occurs}
- Untreated children → fail to thrive → die in 4/5 years
  - hair on end appearance on x ray. Chipmunk facies.
  - splenomegaly – Extramedullary hematopoiesis. hepatomegaly.
  - Iron overload → hemosiderosis & secondary hemochromatosis.

- ∆ peripheral blood

Peripheral Blood Smear (figure)

RBC
- Microcytic hypochromic RBC
- marked anisopoikilocytosis → severe
- Target cell
- nucleated RBC (normoblasts)
- tear drop cell
- Basophilic stippling.

WBC → leukocytosis – mild left shift

platelet → Normal.

Bone marrow findings (look at text wrong format)

cellularity – markedly hypercellular; M:E ratio ☆

- normoblastic erythroid hyperplasia (erythropoiesis)

↓

Markedly hypercellular.

- myelopoiesis, megakaryopoiesis – N.
- Bone marrow iron.

↓

Markedly ↓ due to ↑ decay absorption and hemolysis.

↓

siderotic granules in cytoplasm of normoblasts. (nucleated RBC)

S.A

Lab Investigations to Establish the diagnosis → Hb ✓ Electrophoresis / HPLC

1. Anemia – Severe Hb 3–8 g/dL.
2. Blood smear – microcytic hypochromic RBC, target cells, normoblast, teardrop.
3. Serum Bb → unconjugated is raised
4. Reticulocytosis, RBC ↑ / Normal.
5. MCV, MCH, MCHC are significantly reduced
6. WBC ↑, shyllo left
7. platelet count normal. ☆
8. ↓ Osmotic fragility.
9. ↑ HBA_2, HBF. ↓ or (-) of HBA

↑ HBA_2 → not in any other Hb abnormality except thalassemia.

10. Bone marrow aspirate exam
    - → normoblastic erythroid hyperplasia
    - → ↑ iron.

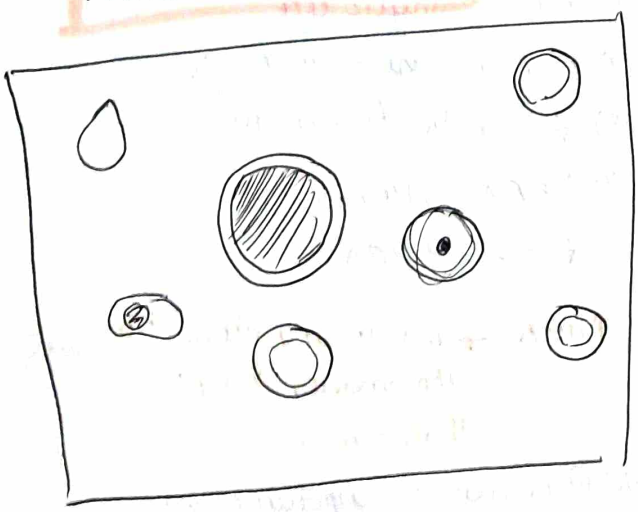
Peripheral Blood.

- Hb - 3-8 g/dL and Hematocrit - 8-23%.] Markedly reduced
- RBC → count is increased ↑ normal.
- Reticulocyte Count → ↑
  ↑ and in range of ~~60~~%.

Red cell Indices

- MCV - decreased - < 70 fL
  Normally (82-98 fL).
- MCH - decreased. - 20-28 pg.
  N - 27-32 pg.
- MCHC - (decreased. - 22-30 g/dL.
  (N - 31-35 g/dL)

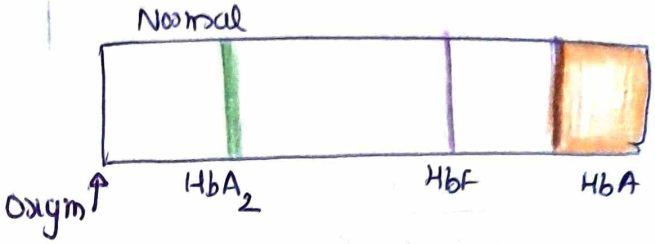
MCV - 82-98 fL
MCH - 27-32 pg
MCHC - 31-35 g/dL

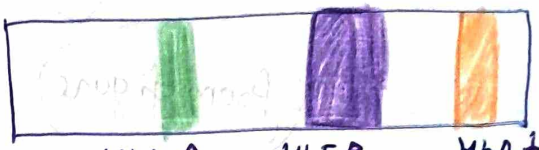


Special Diagnosis

① HBF (fetal) increased.

② Hb electrophoresis.





Biochemical findings

→ Bilirubin → unconj ↑.
→ UBG - ↑.
→ haptoglobin ↓.

Iron status:
serum iron, serum ferritin, transferrin saturation are markedly increased.

→ TIBC - ↓.

Special test

- Hb Electrophoresis
- High performance liquid chromatography - HPLC.
  for confirmation of diagnosis.

pathogenesis.