Hemoglobinopathies

- Altered structure, function, or production.
- Usually inherited.

- Range in severity from asymptomatic laboratory abnormalities to death in utero.
- Different hemoglobins are produced during embryonic, fetal, and adult life.
Properties of the Human Hemoglobin

• Hemoglobin critical - oxygen delivery.
• Can alter red cell shape, deformability, and viscosity.
• Tetramer – bind up to 4 $O_2$
• $2\alpha$ chains (141 amino acids) & $2\beta$ chains (146 amino acids).
Properties of the Human Hemoglobins

- HbA1(α2 β2) - major adult
- HbA2(α2δ2) - minor
- HbF(α2γ2)
- Hemoglobin tetramer - highly soluble but individual globin chains are insoluble.
- Unpaired globin precipitates, forming inclusions that damage the cell.
Function of Hemoglobin

• oxygen transport
• Bind $O_2$ efficiently & retain at high $O_2$ tension (alveolus).
• Release at low $O_2$ tension(tissue).
• cooperativity or heme-heme interaction
• Bohr effect (ability of hemoglobin to deliver more oxygen to tissues at low pH)
Hemoglobin-oxygen dissociation curve


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Classification of Hemoglobinopathies

I. **Structural hemoglobinopathies**—hemoglobins with altered amino acid sequences eg HbS

II. **Thalassemias**—defective biosynthesis of globin chains

III. **Thalassemic hemoglobin variants**—structurally abnormal Hb associated with co-inherited thalassemic phenotype HbE, Hb Constant Spring, Hb Lepore

IV. **Hereditary persistence of fetal hemoglobin**

V. **Acquired hemoglobinopathies**
   A. Methemoglobin
   B. Sulfhemoglobin
   C. Carboxyhemoglobin
   D. HbH in erythroleukemia
Sickle cell syndrome

• Mutation in β globin gene that changes sixth amino acid from glutamic acid to valine
• HbS polymerises reversibly when deoxygenated, to form a gelatinous network of fibrous polymer that stiffens the erythrocyte membrane, ↑viscosity. These changes produce characteristic sickle shape- prone to hemolysis

Classification
• Homozygous SS sickle cell anaemia
• Heterozygous AS sickle cell trait (generally asymptomatic – protects against falciparum malaria)
Factors increasing sickling

- Hypoxia
- Low pH
- Fever
- Infection
- Excess exercise
- Anxiety, dehydration
- Abrupt tem. changes
Pathophysiology of sickle cell crisis

- Arterial PO₂, oxy Hbs (soluble) → Capillary venous PO₂, deoxy Hbs (polymerized)
- Stiff, viscous sickle cell → Membrane changes, Ca²⁺ influx, K leakage
  - Capillary venule occlusion
  - Shortened red cell survival (hemolytic anemia)
- Microinfarction, Ischemic tissue pain, Ischemic organ malfunction, Autoinfarction of spleen
- Anemia, Jaundice, Gallstones, Leg ulcers


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Clinical features

- Anaemia
- Jaundice
- Splenomegaly
- Painful swelling hands & feet
- Chronic lower leg ulcers probably arise from ischemia and super infection in the distal circulation.

- Constitutional symptoms - impaired growth
  ↑susceptibility to infection
Clinical features

• **Vasooclusive phenomenon**
• Microinfarct – abdomen, chest pain, back pain, joints (recurrent painful crises)
• These recurrent episodes, called *painful crises*, are the most common clinical manifestation.
• Macroinfarct – splenic sequestration crisis (autosplenectomy)
  - Bone marrow infarct
  - Bone aseptic necrosis, osteomyelitis
  - Renal cortical necrosis
  - *hand-foot syndrome*
  - priapism
  - CNS – stroke
    - Retinal damage – blindness
    - Skin ulcers
  - *Acute chest syndrome*
Investigation

- Diagnosis is usually established in childhood,
- childhood history
- hemolytic anemia
- Granulocytosis
- RBC morphology - sickle cell, target cell, howell-jolly body
- intermittent episodes of ischemic pain
- Diagnostic test- Sickling test +ve with reducing substance as sodium metabisulfite
- Hb electrophoresis (HbS)
Factors associated with increased morbidity and reduced survival

- > three crises requiring hospitalization per year.
- chronic neutrophilia.
- a history of splenic sequestration or hand-foot syndrome, and second episodes of acute chest syndrome
Treatment

• Patient require ongoing continuity of care.
• Education and familiarity with pattern of symptoms provide the best safeguard.
• Treatment of ppt factors
• preventive measures- regular slit-lamp examinations
• antibiotic prophylaxis appropriate for splenectomized patients during dental or other invasive procedures; and
• vigorous oral hydration during or in anticipation of periods of extreme exercise, exposure to heat or cold, emotional stress, or infection.
• Pneumococcal and Haemophilus influenzae vaccines.
Treatment

• **management of acute painful crisis** - vigorous hydration, thorough evaluation for underlying causes (such as infection), and aggressive analgesia, blood transfusion should be reserved for extreme cases.

• **Acute chest syndrome** medical emergency that may require management in an intensive care unit oxygen therapy, Hydration transfusion to maintain a hematocrit > 30, and emergency exchange transfusion if arterial saturation drops to <90%.
Treatment

- **Hydroxyurea** - (10–30 mg/kg per day) increases fetal hemoglobin and may also exert beneficial affects on RBC hydration, vascular wall adherence, and suppression of the granulocyte and reticulocyte counts; dosage is titrated to maintain a white cell count between 5000 and 8000 per L.

- **BMT** - definitive cures known to be effective and safe only in children. Prognostic features justifying bone marrow transplant are the presence of repeated crises early in life, a high neutrophil count, or the development of hand-foot syndrome.

- Gene therapy
Thalassemia syndrome

Hemoglobin consist of 2α & 2β peptide chains

HbA 95% – α2β2
HbA 2 5%  -  α2 δ2
Fetal HbF -  α2 γ2
(may persist in β thalasemia)
Thalassemia syndrome

- At birth, Hgb F appx. 80 % and Hgb A -20 %.

- By approximately six months of age, healthy infants will have transitioned to mostly Hgb A, a small amount of Hgb A2, and negligible Hgb F
Blood film of thalassemia
Epidemiology

- Affects men and women equally and occurs in approximately 4.4 of every 10,000 live births.
- Alpha thalassemia occurs most often in persons of African and Southeast Asian descent.
- Beta thalassemia is most common in persons of Mediterranean, African, and Southeast Asian descent.
- Thalassemia trait affects 5 to 30 percent of persons in these ethnic groups.
Alpha Thalassemia

- Alpha thalassemia is the result of deficient or absent synthesis of alpha globin chains, leading to excess beta globin chains.

- Alpha globin chain production is controlled by two genes on each chromosome 16.
Beta Thalassemia

- Beta thalassemia is the result of deficient or absent synthesis of beta globin chains, leading to excess alpha chains.

- Beta globin synthesis is controlled by one gene on each chromosome 11
## Classification of thalassemia

<table>
<thead>
<tr>
<th>Type</th>
<th>Hb g/dl</th>
<th>Hb-Electrophoresis</th>
<th>Clinical Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>α- thalassaemias</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydrops foetalis</td>
<td>3-10</td>
<td>Hb Barts(γ4)100%</td>
<td>Fatal in utero/early pregnancy</td>
</tr>
<tr>
<td>Hb-H disease</td>
<td>2-12</td>
<td>HbF(10%)</td>
<td>Hemolytic anaemia</td>
</tr>
<tr>
<td>α- thalassaemias</td>
<td>10-14</td>
<td>N</td>
<td>No anemia (RBC-MH)</td>
</tr>
<tr>
<td>β- thalassaemias</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>β- thalassaemias major</td>
<td>&lt;5</td>
<td>HbA(0-50%) HbF(50-98%)</td>
<td>Severe congenital HA/require BT</td>
</tr>
<tr>
<td>β- thalassaemias intermedia</td>
<td>5-10</td>
<td>Variable</td>
<td>Severe anaemia</td>
</tr>
<tr>
<td>β- thalassaemias minor</td>
<td>10-12</td>
<td>HbA2(4-9%) HbF(1-5%)</td>
<td>Mostly asymptomatic</td>
</tr>
</tbody>
</table>
α- thalassemias

Hb Barts- Hydrops foetalis

• deletion of all four α chain genes
• Total suppression of α globin chain synthesis
• Most severe form (Homozygous state)
• Incompatible with life
• Diagnosis-lab picture of severe HA
• Hb-Electrophoresis- Hb Barts - diagnostic
Hb-H disease

- Deletion of three α-chain genes
- Hb-H β-globin chain tetramer(β4)
- Markedly impaired α-chain synthesis
- Clinical feature- s/o HA
- Lab- hemolytic anemia, Heinz bodies(brilliant cresyl blue stain)
- Diagnostic-Hb-Electrophoresis
β- thalassemias

β- thalassemia major

- Common form of congenital anemia
- Homozygous form characterized by complete absence of β chain synthesis
- Diagnosis-lab picture of severe HA
- Hb-Electrophoresis-HbF & HbA2 - diagnostic
Severity of β-Thalassemia

- Homozygous disorder
- Significant imbalance of α/β-globin chains
- Severe anemia presenting early in life
- Requires lifelong RBC transfusions
- If untreated (i.e. no HSCT or supportive care),
  leads to death usually in first decade

- Various genetic interactions
- Globin-chain production moderately impaired
- Mild anemia, diagnosed usually in late childhood
- Occasional blood transfusions may be required

- Heterozygous condition
- Asymptomatic
- May require genetic counselling

β-Thalassemia
- major
- intermedia
- minor

Severity of disease
Clinical features

• Anemia
• Marked hepatosplenomegaly
• Marrow hyperplasia  frontal bossing & prominent malar eminence
• Chipmunk facies, thalassemic facies
• Iron overload
• Growth retardation
• Delayed puberty, DM
• Cardiomegaly
Chipmunk facies, thalassemic facies
maxillary marrow hyperplasia and frontal bossing
Time of complications of Thalassemia
Diagnosis

• Most persons with thalassemia trait are found incidentally when their complete blood count shows a mild microcytic anemia

Microcytic anemia can be caused by:
1. Iron deficiency
2. Thalassemia
3. Lead poisoning
4. Sideroblastic anemia
5. Anemia of chronic disease.
# Use of RDW Values in the Diagnosis of Thalassemia

<table>
<thead>
<tr>
<th>Microcytic Anemia</th>
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</thead>
<tbody>
<tr>
<td>Children 6 months - 6 years of age: MCV &lt;70fl</td>
</tr>
<tr>
<td>Children 7 to 12 years of age: MCV &lt;76fl</td>
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</tbody>
</table>

<table>
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<tr>
<th>RDW</th>
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<table>
<thead>
<tr>
<th>Normal</th>
<th>Elevated (&gt;15)</th>
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<td>↓</td>
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<table>
<thead>
<tr>
<th>Favors Thalassemia</th>
<th>Ferritin level</th>
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<table>
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<tr>
<th>Normal (&gt;100ng/mL)</th>
<th>Low (&lt;10ng/mL)</th>
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<th>Favors Thalassemia</th>
<th>Favors Iron Deficiency anemia</th>
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</table>
Supplemental tests

• Include:
  - Serum ferritin
  - The peripheral smear
  - Hemoglobin electrophoresis
  - Serum lead level
  - Rarely bone marrow aspirate
The hemoglobin electrophoresis
Treatment

- Blood transfusion to maintain hematocrit
- Folate supplementation
- Avoid iron therapy
- Desferrioxamine for iron chelation
- Splenectomy
- Allogenic bone marrow transplantation
- Gene therapy
- Antenatal diagnosis of thalassemia syndromes is now widely available.
- DNA diagnosis is based on PCR amplification of fetal DNA, obtained by amniocentesis or chorionic villus biopsy.
Prevention

• Blood tests and family genetic studies can show whether an individual has thalassemia or is a carrier.

• A genetic counselor can detail the family background, discuss risks.