1. Background

a) Definitions
   - Thalassemia is a congenital disorder characterized by the deficient synthesis of one or more of the globin polypeptide chains that result in an imbalance between numbers of alpha and beta globin chains. The end result is ineffective erythropoiesis, hypochromic RBCs, microcytosis and hemolysis which consequently lead to anemia. The severity depends on the number and type of mutations present.
   - As a group, thalassemias are the most common single genetic disorder known.
   - Thalassemias are named according to the deficient chain.

b) Background Physiology
   - Normal adult Hb A is composed of 2 alpha and 2 beta chains. In a normal genotype there are two copies of the alpha globin gene on each chromosome 16 (e.g. αα/αα); there is 1 copy of the beta globin gene on each chromosome 11 (e.g. β/β).
   - The clinical spectrum of disease results from the heterogeneity of genetic mutations, genetic combinations and inherited confounding cofactors that can affect the globin genes.
   - Bone marrow transplantation is the only existing cure for severe thalassemia.
   - Most alpha thalassemia cases result from gene deletions. In general, these deletions result in an excess of beta chains which form tetramers [hemoglobin H] that precipitate causing damage to the red blood cell’s membrane. Because there are 4 genes and thus 4 different possibilities of copy number, 4 major variants of alpha thalassemia exist:
- Alpha thalassemia 2 trait, also called the silent carrier is an asymptomatic carrier of a single alpha gene deletion (α α / α -).

- Alpha thalassemia 1 trait results from deletions of 2 of the alpha gene and commonly is a subclinical anemia (α α / - - or α - / α -).

- Hb H disease results from 3 deletions of the alpha genes and has a clinical correlate of moderate to severe hemolytic anemia (α - / - -).

- Hydrops fetalis with Hb Bart’s results from an absence of alpha genes (- - / - -) and causes severe anemia and death in utero or shortly after birth.

- Most beta thalassemia cases result from nucleotide deletions or substitutions. In general, this results in an excess of alpha globins that form insoluble tetrameric inclusions in the red blood cells. There are 3 main types of Beta thalassemia:

  - Beta thalassemia major [Cooley’s] which is a severe disease presenting in early infancy [4-6 months] caused by defects in both copies of the Beta globin gene (β° / β°).

  - Beta thalassemia intermedia is a less severe anemia caused by several genetic combinations (β+ / β+ and others).

  - Beta thalassemia minor, which is a mild, non-transfusion dependent anemia is caused by a defect in one copy of the Beta gene. Beta thalassemia trait has one Beta gene defect (β / β°) whereas a silent carrier form exists where some functional beta thalassemia gene is produced (β / β+).

### Alpha Thalassemia

### Beta Thalassemia

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Genotype</th>
<th>MCV</th>
<th>Anemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Silent carrier (2 trait)</td>
<td>α α / α -</td>
<td>Normal</td>
<td>None</td>
</tr>
<tr>
<td>Trait (1 trait)</td>
<td>α α / - - or α - / α -</td>
<td>Low</td>
<td>Mild</td>
</tr>
<tr>
<td>Hb H disease</td>
<td>α - / - -</td>
<td>Low</td>
<td>Moderate</td>
</tr>
<tr>
<td>Major (hydrops fetalis)</td>
<td>- - / - -</td>
<td>Low</td>
<td>Fatal</td>
</tr>
</tbody>
</table>

**Disorder** | **Genotype** | **MCV** | **Anemia**
--- | --- | --- | ---
Silent carrier | β/ β+ | Low | Mild
Trait | β/ β° | Low | Mild
Intermedia | β+ / β+ | Low | Moderate
Major | β° / β° | Low | Severe
MCV = mean corpuscular volume; \( \beta^+ \) = thalassemic gene producing some beta chain; \( \beta^\circ \) = thalassemic gene producing no beta chain

2. Questions to ask

a) **General signs of anemia**
   - Tiredness, irritability, breathlessness and poor exercise tolerance

b) **Abdominal pain or masses**
   - Splenomegaly and cholelithiasis

c) **Heart failure signs**
   - Dyspnea, orthopnea, abdominal swelling and peripheral edema

d) **Symptoms that may suggest Sickle cell**
   - Crisis: pains in stomach and joints
   - Priapism
   - Gallstones

e) **Symptoms that may suggest G6PD**
   - Concurrent infection triggering the hemolysis
   - Jaundice at birth [also suggest red cell membrane disorders]

f) **Drugs**
   - Some drugs can cause hemolysis

g) **When did they start to become unwell**
   - Beta thalassemia tends to present around 6 months of age

h) **Family history**
   - Often there exists a family history of anemia
   - Consanguinity
   - Alpha thalassemia is most common in those of Asian decent.
   - Beta thalassemia is most common in those of Mediterranean descent, especially those from Greece and Italy. Also found in Africa, India and Asia.

i) **Past medical History**
   - Chronic anemia, iron therapy, iron chelation, blood transfusions, jaundice, splenectomy, bone marrow transplant

j) **Diet**
   - Folic acid and zinc frequently require supplements due to high RBC turnover
   - Watch out for iron overload

3. Differential diagnosis

- Iron deficiency anemia
- Other hemoglobinopathies [ex. Sickle cell]
- Other hemolytic anemias [ex. G6PD deficiency, pyruvate kinase deficiency, congenital spher- or elliptocytosis, autoimmune and infectious]

4. Physical Examination

a) One should examine the following
- **Vitals**
  - Temperature, especially in children who have had a splenectomy
  - Heart rate as may be tachycardic if significant anemia
  - Blood pressure, oxygen saturation, respiratory rate
  - Growth parameters as can often exhibit poor growth

- **Abdomen**
  - Splenomegaly and hepatomegaly
  - Abdominal pain due to splenic infarct
  - RUQ pain due to cholelithiasis

- **Skin**
  - Cyanosis
  - Pallor of skin, lips or nail bed
  - Jaundice

- **Cardiac**
  - Systolic ejection murmur in severe anemia

- **Facial**
  - Maxillary hyperplasia, dental malocclusion

- **Endocrine**
  - Iron overload can be toxic to endocrine glands leading to their dysfunction and a spectrum of symptoms including growth retardation and delayed or absent sexual development.

- **MSK**
  - Pathological fracture and osteoporosis due to extramedullary erythropoiesis

5. Investigations

a) **Laboratory investigations**
- CBC
- Peripheral blood smear
- Hemoglobin electrophoresis
- Serum ferritin, transferring and TIBC
- Serum bilirubin, urine urobilin and urobilinogen
- Liver function tests
- Genetic analysis of globin chain genes

b) **Imaging Studies**
- Not routine
- US of spleen
- MRI analysis of myocardial iron content in heart failure
- Regular plain film X-rays of vertebrae and extremities if on Deferoxamine therapy
- Other highly specialize studies

References

Acknowledgements
Writer: Giulio S. Dominelli

<table>
<thead>
<tr>
<th>Thalassemia type</th>
<th>Genetics</th>
<th>Clinical correlate and Hematologic features</th>
</tr>
</thead>
<tbody>
<tr>
<td>α-thalassemias</td>
<td></td>
<td></td>
</tr>
<tr>
<td>α silent carrier</td>
<td>-α/αα</td>
<td>Normal: Mild microcytosis</td>
</tr>
<tr>
<td>α trait</td>
<td>-α/-α or αα/--</td>
<td>Usually normal: Microcytosis, hypochromia, mild anemia</td>
</tr>
<tr>
<td>HbH disease</td>
<td>--/α-</td>
<td>Thalassemia intermedia: Microcytosis, inclusion bodies, moderate to severe anemia</td>
</tr>
<tr>
<td>Hydrops fetalis</td>
<td>--/--</td>
<td>Stillborn or neonatal death: Anisocytosis, poikilocytosis, severe anemia</td>
</tr>
</tbody>
</table>

| β-thalassemias   |          |                                             |
| β°-homozygous   | β°/β°     | Cooley anemia: Severe anemia, normoblastemia |
| β⁺ homozygous   | β⁺/β⁺     | Thalassemia Intermedia: Anisocytosis, poikilocytosis, moderate to severe anemia |
| β°-heterozygous | β°/β      | Splenomegaly, jaundice: Microcytosis, hypochromia, mild to moderate anemia |
| β -silent carrier | β/β⁺     | Normal: Microcytosis, hypochromia, mild anemia |