Microcytic Anemia: Thalassemia (Alpha and Beta Thalassemia)

Thalassemia is a major cause of microcytic anemia due to an imbalance in the production of α or β-globin. α-thalassemia results from a deficiency of α-chains. β-thalassemia results from the deficiency of β-chains. The treatment, if required, involves blood transfusion.

Definition of Thalassemia

Thalassemia is microcytic-hypochromic anemia. It is caused by the decreased synthesis of 1 or several globin chains. Since globin synthesis is flawed, the disease is 1 of the so-called hemoglobinopathies. Depending on which globin chain is affected by the disorder, one speaks of α- or β-thalassemia.

Thalassemias are caused by gene mutations leading to the decreased production of globin protein. Deletions of α-globin genes cause α-thalassemia. There are 2 α-globin genes closely linked on chromosome 16 and a total of 4 alleles.
Epidemiology of Thalassemia

Since thalassemia more frequently occurs in the Mediterranean area, including Turkey, it is also referred to as ‘Mediterranean anemia.’ However, it can be found worldwide. It is estimated that approx. 3% of the global population carries at least 1 β-thalassemia gene.

Etiology of Thalassemia

Thalassemia is an inherited **autosomal-codominant**. A milder form of the disease develops with heterozygosity (minor thalassemia) whereas the severe form (major thalassemia) can be observed with homozygosity. There is also an **intermediate thalassemia** form. The primary causes are genetic defects, which form the pathogenetic basis of the decreased synthesis of 1 of several polypeptide chains of the globin molecule.

In turn, this results in a decreased hemoglobinization of the erythroblasts. In the blood count, this condition can be observed as hypochromasia of the erythrocytes. Additionally, the globin chains, which continue being produced, aggregate and make for increased apoptosis of precursor cells via different pathophysiological mechanisms. This condition also leads to a decreased lifespan of the erythrocytes in the peripheral blood.

**α-thalassemia**
The characteristics and severity of the disease depend on the number of genes deleted:

<table>
<thead>
<tr>
<th>Disease</th>
<th>Genotype</th>
<th>Clinical manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Silent carrier</td>
<td>-α/αα</td>
<td>Asymptomatic</td>
</tr>
<tr>
<td>α-thalassemia trait</td>
<td>-/αα</td>
<td>Asymptomatic, with mild anemia</td>
</tr>
<tr>
<td>-α/-α</td>
<td></td>
<td>Intermediate-to-severe chronic anemia</td>
</tr>
<tr>
<td>HbH disease</td>
<td>-/–</td>
<td>Pre or neonatal lethality</td>
</tr>
<tr>
<td>Hydrops fetalis</td>
<td>-/-</td>
<td></td>
</tr>
</tbody>
</table>

Hemoglobin electrophoresis

Image: The pictograph shows 1 example of how α-thalassemia is inherited. The α-globin genes are located on chromosome 16. A child inherits 4 α-globin genes (2 from each parent). In this example, the father is missing 2 α-globin genes and the mother is missing 1 α-globin gene. Each child has a 25% chance of inheriting 2 missing genes and 2 normal genes (thalassemia trait), 3 missing genes and 1 normal gene (hemoglobin H disease), 4 normal genes (no anemia), or 1 missing gene and 3 normal genes (silent carrier). By National Heart Lung and Blood Institute, License: Public domain

Image: Hemoglobin electrophoresis. By Lecturio
Newborns: Splenic macrophages phagocytose and destroy red blood cells (RBCs) with fetal hemoglobin (HbF) and replace them with hemoglobin A (HbA) and hemoglobin A2 (HbA₂), which takes a few months.

Anemia, but no change in % of Hb A, A₂ or F (all of them need α-globin chains for their synthesis).

β-thalassemia
There is only 1 β-globin gene on chromosome 11, a total of 2 alleles. β-thalassemia is primarily caused by splicing mutations in β-globin genes.

**There are 2 types of mutations in the β-globin gene:**

- β⁺ mutations – variable decreased expression
- β mutations – absent expression

**This results in 3 different clinical syndromes:**

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Genotype</th>
<th>Clinical features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thalassemia minor</td>
<td>β/β or β⁺/β</td>
<td>Asymptomatic; mild anemia</td>
</tr>
<tr>
<td>Thalassemia intermedia</td>
<td>β/β or β⁺/β⁺</td>
<td>Variable moderate anemia, requiring occasional transfusion</td>
</tr>
<tr>
<td>Thalassemia major a.k.a. Cooley’s anemia</td>
<td>β/β or β⁺/β⁺</td>
<td>Severe, transfusion-dependent anemia</td>
</tr>
</tbody>
</table>

**Clinical Features of Thalassemia**

Depending on the genetic defect, thalassemia shows a variable clinical picture.

**Minor thalassemia** usually does not show severe symptoms. Slight hepatosplenomegaly and possibly recurrent jaundice in a mild form can be present. Also, target cells can be observed in the blood count.

In its more distinct form, that is major thalassemia, the disease can lead to bone deformations, and even fractures, due to the reactive expansion of erythropoiesis in the bone marrow. Because of the decreased, and often pathological erythrocytes, hypoxia becomes clinically relevant as growth disturbances and trophic skin changes are
observed during childhood.

**α-thalassemia**

**There are 2 consequences of decreased α-globin production:**

- Decreased hemoglobin synthesis, causing microcytic, hypochromic anemia
- The quantitative imbalance between α- and β-globin proteins, resulting in the formation of insoluble β-globin (HbH) or γ-globin (Hb Barts) aggregates in the RBC. These RBCs are often cleared in the spleen and liver, worsening the anemia.

It is most common in patients of Southern Asian (-α allele) and African (-α allele) descent.

**HbH disease**

- Signs and symptoms of anemia
- Chronic hemolysis with variable jaundice and cholelithiasis (bilirubin stones)
- Extramedullary hematopoiesis with frontal bossing and hepatosplenomegaly

**Hydrops fetalis**

- Anasarca (generalized edema) from high-output heart failure
- Hepatosplenomegaly
- Causes death in the prenatal period

**β-Thalassemia**

Similar to α-thalassemia.

- AR (androgen receptor) disorder: Africans, Italians, Greeks
- → RBC count: splicing defect for the minor; nonsense mutation for major (stop codon).

\[ \begin{align*}
\beta &= \text{normal} \\
\beta^+ &= \text{some} \\
\beta &= \text{none}
\end{align*} \]
**Note that HbA is decreased because β-globin chain synthesis is decreased. There is a corresponding increase in HbA₂ and HbF.**

**Note that there is no synthesis of HbA.**

### β-Thalassemia major (Cooley’s anemia)

**Laboratory findings:**
- Decreased hemoglobin (Hgb), hematocrit (Hct), and mean corpuscular volume (MCV)
- Variable RBC count
- Hemoglobin electrophoresis varies depending on the severity of the disease, with decreased HbA, increased HbF ($\alpha_2\gamma_2$) and increased HbA₂ ($\alpha_2\delta_2$)

It causes severe transfusion-dependent anemia that develops at a few months of age (as HbF declines). If adequately transfused, children will develop normally but will develop secondary hemochromatosis and die of heart disease in their 20s. If not transfused, there is stunted growth, bony changes, and high-output heart failure with death in infancy.

### Diagnosis of Thalassemia

The blood count of minor thalassemia shows microcytic, hypochromic erythrocytes. Since this is also the case with iron deficiency and this condition is more frequent in practice, one should consider minor thalassemia when confronted with a non-confirmed iron deficiency anemia. A blood smear with target cells and poikilocytosis provides additional certainty.

- **Laboratory studies:** decreased Hgb, Hct, MCV; increased RBC count, red cell distribution width (RDW); HbH on hemoglobin electrophoresis; iron studies normal.

In major thalassemia and intermediate thalassemia, hypochromasia, and poikilocytosis are more distinct. Reticulocytes, lactate dehydrogenase (LDH), and bilirubin are increased; haptoglobin is decreased.

Further criteria confirming the suspicion are positive family history, disturbed hemoglobinization in bone marrow aspirate, and genome analysis.
Therapy of Thalassemia

The ideal therapy is allogeneic stem cell transplantation. Since the minor form does not usually require treatment, this primarily applies to major thalassemia.

Course and Prognosis of Thalassemia

If the anemia is not treated adequately, there is a massive expansion of hemopoiesis within the bone marrow. This can lead to a ‘hair on end’ appearance on skull X-ray. If regular transfusions are given, iron chelation must be started.

While minor and intermediate thalassemia mostly progresses without complications, major thalassemia during infancy can lead to death if not treated. Another life-shortening factor is increased iron accumulation (hemosiderosis), which is why iron supplementation is contraindicated in cases of thalassemia.

Note: Thalassemia is microcytic, hypochromic anemia caused by a genetically-based decreased synthesis of 1 or several globin chains. It is classified into 3 forms: minor thalassemia, major thalassemia, and intermediate thalassemia. In a blood smear, the target cells can be seen. In differential diagnoses, thalassemia must not be confused with iron deficiency anemia since iron substitution in the case of thalassemia falsely diagnosed as iron deficiency anemia leads to increased hemosiderosis.

References


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