**Genetic Diseases**

**Lecture 5**

**THALASSEMIA**

Thalassemia is forms of inherited autosomal recessive blood disorders that originated in the Mediterranean region (in Greek, Thalassa is for the sea, Haema is for blood) ). Thalassemia is the name of a group of genetic blood disorders characterized by anemia due to enhanced RBC destruction. In thalassemia, the disease is caused by the weakening and destruction of red blood cells. Thalassemia is caused by variant or missing genes that affect how the body makes hemoglobin.

Hemoglobin is the protein in red blood cells that carries oxygen. People with thalassemia make less hemoglobin and fewer circulating red blood cells than normal, which results in mild or severe anemia.

Thalassemia is a quantitative problem of too few globins synthesized, whereas sickle-cell anemia (a hemoglobinopathy) is a qualitative problem of synthesis of an incorrectly functioning globin. Thalassemias usually result in underproduction of normal globin proteins,often through mutations in regulatory genes. Hemoglobinopathies imply structural abnormalities in the globin proteins themselves. The two conditions may overlap, however, since some conditions which cause abnormalities in globin proteins (hemoglobinopathy) also affect their production (thalassemia).Thus, some thalassemias are hemoglobinopathies, but most are not. Either or both of these conditions may cause anemia.

**CAUSES [ETIOLOGY]**

Normal hemoglobin, also called hemoglobin A, has four protein chains—two alpha globin and two beta globin. The two major types of thalassemia, alpha and beta, are named after defects in these protein chains. Four genes are needed to make enough alpha globin protein chains. Alpha thalassemia trait occurs when one or two of the four genes are missing. If more than two genes are missing, the result is moderate to severe anemia. The most severe form of alpha thalassemia is known as alpha thalassemia major or hydrops fetalis. Babies with this disorder usually die before or shortly after birth. Two genes (one from each parent) are needed to make enough beta globin protein chains. Beta thalassemia occurs when one or both genes are altered. The severity of beta thalassemia depends on how badly one or both genes are affected. If both genes are affected, the result is moderate to severe anemia.

**Pathophysiology**

Normally, hemoglobin is composed of four protein chains, two α and two β globin chains arranged into a heterotetramer. In thalassemia, patients have defects in either α or β globin chain (unlike sickle-cell disease, which produces a specific mutant form of β globin), causing production of abnormal red blood cells.

**Classification**

The **thalassemias** are classified according to which chain of the hemoglobin molecule is affected. In α thalassemias, production of α globin chain is affected, while in β thalassemia production of the β globin chain is affected. The β globin chains are encoded by a single gene on chromosome 11; α globin chains are encoded by two closely linked genes on chromosome 16. Thus, in a normal person with two copies of each chromosome, there are **two** loci encoding the β chain, and **four** loci encoding the α chain. Deletion of one of the α loci has a high prevalence in people of African or Asian descent, making them more likely to develop α thalassemias. β Thalassemias are not only common in Africans, but also in Greeks and Italians.

**GLOBIN CHAIN PRODUCTION**

To understand the genetic changes that result in thalassemia, one should be familiar with the physiologic process of globin chain production in the healthy individual. The globin chain as a unit is a major building block for Hb: together with heme, it produces the Hb molecule (heme plus globin equals Hb). Two different pairs of globin chains form a tetrameric structure with a heme moiety in the center. All normal Hbs are formed from 2 α-like chains and 2 non-α chains.

**MOLECULAR BIOLOGY**

Each globin gene consists of a string of nucleotide bases divided into 3 coding sequences, termed exons, and 2 noncoding regions, known as introns or intervening sequences (IVS).



**MOLECULAR PATHOLOGY**

To date, more than 1000 inherited mutations that affect either the structure or synthesis of the α- and β-globin chains are known. Mutations that result in β or α thalassemia are similar in principle but different in their patterns. Presently, more than 200 molecular defects known to down regulate the expression of β globin have been characterized. Such defects result in various types of β thalassemia.

**GENETIC CHANGES**

All the genes that control the production of globin chains lie within 1 of 2 clusters located on 2 different chromosomes. Chromosome 11 is the site of 5 functional b-like globin genes arranged in a link cluster over 60 kilobases (kb). A critical control region of the d-globin gene (promoter) is known to be defective; it inhibits messenger RNA (mRNA) processing, resulting in only a small amount of Hb A2 (α2/δ2) production, which thus accounts for less than 3% of total Hb in adult RBCs. The α-like globin gene cluster is located on chromosome 16 and consists of 3 functional genes. From left to right (5'-3'), the genes are α/α2/α1.

**TYPES OF THALASSEMIAS**

***a.*****Alpha Thalassemias**

People whose hemoglobin does not produce enough alpha protein have alpha thalassemia. Four genes (two from each parent) are needed to make enough alpha globin protein chains. If one or more of the genes is missing, one will

have alpha thalassemia trait or disease. This means that one don't make enough alpha globin protein. If one has only 1 missing gene, you're a silent carrier and won't have any signs of illness. If one have 2 missing genes, one have alpha thalassemia trait (also called alpha thalassemia minor). One may have mild anemia. There are four subtypes of alpha thalassemia. Each type represents the loss of or damage to one, two, three, or four genes.

**One gene**: If one alpha-globin gene is missing or damaged, one will have no symptoms and will not need treatment. But he/she is a **silent** **carrier**. This means one doesn’t have the disease but one can pass the defective gene

onto your child. Smaller-than-normal blood cells may be the only sign of the condition.

**Two** **genes**: If two alpha-globin genes are missing or damaged, one will have very mild anemia that will not need treatment. This is known as **alpha** **thalassemia minor** or **alpha thalassemia trait**.

**Three genes**: If three alpha-globin genes are missing, one will have mild to moderately severe anemia. This is sometimes called **hemoglobin H disease**, because it produces heavy hemoglobin. The body removes this heavy hemoglobin faster than it does normal hemoglobin. The more severe forms

may need treatment with blood transfusions.

**Four genes**: If all four alpha-globin genes are missing (**alpha thalassemia major**), the fetus will be stillborn or the child will die shortly after birth.1 The hemoglobin produced by this condition is sometimes called hemoglobin Barts.

***b.*****Beta Thalassemias**

People whose hemoglobin does not produce enough beta protein have beta thalassemia. Two genes (one from each parent) are needed to make enough beta globin protein chains. If one or both of these genes are altered, one will have beta thalassemia. This means that one don't make enough beta globin protein. If one has one altered gene, he/she is a carrier. This condition is called beta thalassemia trait or beta thalassemia minor. It causes mild anemia. There are two subtypes of beta thalassemia. Each type represents the loss of or damage to one & two.

**One gene:** If one of your beta hemoglobin genes is defective, one has mild signs and symptoms. This condition is called betathalassemia minor or as a **beta-thalassemia** **trait**.

**Two genes:** If both of your beta hemoglobin genes are defective, your signs and symptoms will be moderate to severe. This condition is called **beta-thalassemia major** or **Cooley's** **anemia**. Babies born with two defective beta hemoglobin genes usually are healthy at birth, but develop signs and symptoms within the first two years of life.

***c.* Hemoglobin E Beta Thalassemia:**

Hemoglobin E is common abnormal hemoglobin and individuals present a moderately severe anemia which is similar in symptoms to beta thalassemia intermedia**.**

***d.* Hemoglobin H Disease:**

Hemoglobin made from only one gene does not carry oxygen properly. Patients with hemoglobin H disease can suffer from severe anemia.

***e.* Sickle Beta Thalassemia:**

This condition is caused by a combination of beta thalassemia and hemoglobin S and results in RBCs that are defective sickle shaped. The condition varies from moderate to severe type of anemia.

***f.* Delta (δ) thalassemia:**

About 3% of adult hemoglobin is made of alpha and delta chains. Just as with beta thalassemia, mutations can occur which affect the ability of this gene to produce delta chains.

**DIAGNOSIS** ? Will be taken in practical part of the lecture.

**TREATMENT**

Treatments for thalassemias depend on the type and severity of the disorder. Treatment for patients with thalassemia major includes chronic blood transfusion therapy, iron chelation, splenectomy, and allogeneic hematopoietic transplantation.

**Blood Transfusions:** RBCs live for only about 120 days. So, one may need repeated transfusions to maintain a supply of healthy RBCs.

**Iron Chelation Therapy:** Because the hemoglobin in RBCs is an iron-rich protein, regular blood transfusions can lead to a buildup of iron in the blood. This condition is called iron overload. It damages the liver, heart, and other parts of the body. To prevent this damage, iron chelation therapy is needed to remove excess iron from the body. Two medicines are used for iron chelation therapy. Deferoxamine is a liquid medicine that's given slowly under the skin, usually with a small portable pump used overnight. This therapy takes time and can be mildly painful. Side effects include loss of vision and hearing. Deferasirox is a pill taken once a day. Side effects include headache, nausea, vomiting, diarrhea, joint pain, and fatigue.

**Splenectomy:** When the spleen becomes too active and starts to destroy the RBCs, transfusions become less effective. Then it become necessary to take the spleen out called "Splenectomy".

**Folic Acid Supplements:** Folic acid is a B vitamin that helps build healthy Red Blood Cells. One may need to take folic acid supplements in addition to blood transfusions and/or iron chelation therapy**.**

**Blood and Marrow Stem Cell Transplant:** A blood and marrow stem cell transplant replaces your abnormal or faulty stem cells with healthy ones from another person (a donor). Stem cells are the cells inside bone marrow that make RBCs and other blood cells. A stem cell transplant is the only treatment that can cure thalassemia. But only few people are able to find a good match among donors and have the risky procedure.

