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Review Article

THALASSEMIA: A REVIEW

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ABSTRACT:-

The thalassemia is a group of inherited hematologic disorders caused by defects in the synthesis of one or more of the hemoglobin chains. Alpha thalassemia is caused by reduced or absent synthesis of alpha globin chains, and beta thalassemia is caused by reduced or absent synthesis of beta globin chains. Imbalances of globin chains cause hemolysis and impair erythropoiesis. Silent carriers of alpha thalassemia and persons with alpha or beta thalassemia trait are asymptomatic and require no treatment. Alpha thalassemia intermedia, or hemoglobin H disease, causes hemolytic anemia. Alpha thalassemia major with hemoglobin Bart's usually results in fatal hydropsfetalis. Beta thalassemia major causes hemolytic anemia, poor growth, and skeletal abnormalities during infancy. Affected children will require regular lifelong blood transfusions. Beta thalassemia intermedia is less severe than beta thalassemia major and may require episodic blood transfusions. β-Thalassemia and sickle cell disease both display a great deal of phenotypic heterogeneity, despite being generally thought of as simple Mendelian diseases. The reasons for this are not well understood, although the level of fetal hemoglobin (HbF) is one well characterized ameliorating factor in both of these conditions. The globin gene disorders including the thalassemias are among the most common human genetic diseases with more than 300,000 severely affected individuals born throughout the world every year. Because of the easy accessibility of purified, highly specialized, mature erythroid cells from peripheral blood, the hemoglobinopathies were among the first tractable human molecular diseases.

Key words:- *Alpha thalassemia, Beta thalassemia, Hemoglobin*

INTRODUCTION:

Thalassemia is a genetic blood disorder. People with Thalassemia disease are not able to make enough hemoglobin, which causes severe anemia. Hemoglobin is found in red blood cells and carries oxygen to all parts of the body. When there is not enough hemoglobin in the red blood cells, oxygen cannot get to all parts of the body. Organs then become starved for oxygen and are unable to function properly. There are two primary types of Thalassemia disease: Alpha Thalassemia disease and Beta Thalassemia disease. Beta Thalassemia Major (also called Cooley's Anemia) is a serious illness. Symptoms appear in the first two years of life and include paleness of the skin, poor appetite, irritability, and failure to grow. Proper treatment includes routine blood transfusions and other therapies. Thalassemia is a complex group of diseases that are relatively rare in the United States but common in Mediterranean regions and South and Southeast Asia. Worldwide, there

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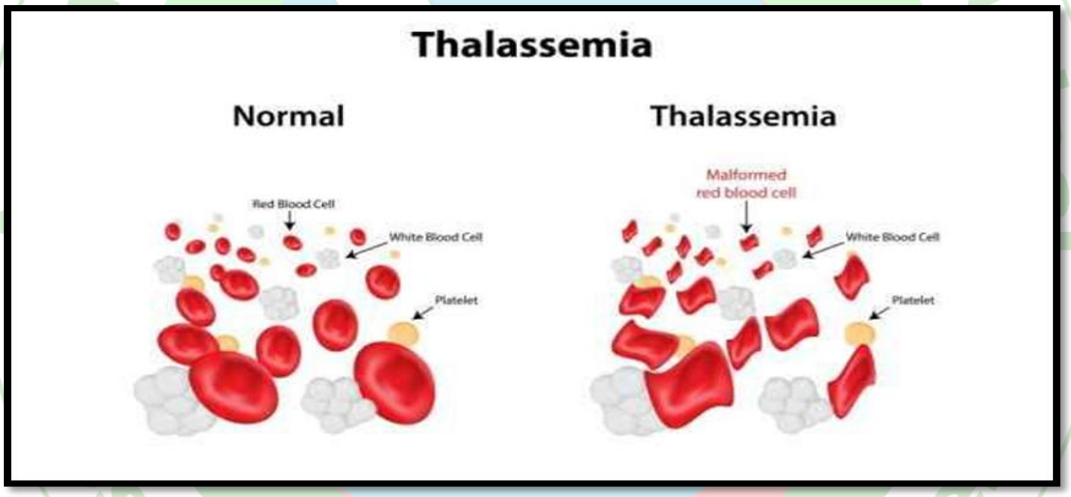
are 350,000 births per year with serious hemoglobinopathies (blood disorders). In the United States, as a consequence of immigration patterns, occurrence of thalassemia disorders is increasing.

The thalassemias are a diverse group of genetic blood diseases characterized by absent or decreased production of normal hemoglobin, resulting in a microcytic anemia of varying degree. The thalassemias have a distribution concomitant with areas where P. falciparum malaria is common. The alpha thalassemias are concentrated in Southeast Asia, Malaysia, and southern China. The beta thalassemias are seen primarily in the areas surrounding Mediterranean Sea, Africa and Southeast Asia. Due to global migration patterns, there has been an increase in the incidence of thalassemia in North America in the last ten years, primarily due to immigration from Southeast Asia. In the normal adult, hemoglobin A, which is composed of two alpha and two beta globins (A^2B^2), is the most prevalent, comprising about 95% of all hemoglobin. Two minor hemoglobins also occur: hemoglobin A_2, composed of two alpha and two delta globins ($\alpha^2 \delta^2$) comprises 2-3.5% of hemoglobin, while hemoglobin F, composed of two alpha and two gamma globins ($\alpha^2 \gamma^2$) comprises less than 2% of hemoglobin. Hemoglobin F, or fetal hemoglobin, is produced by the fetus in utereo and until about 48 weeks after birth. Hemoglobin F has a high oxygen-affinity in order to attract oxygen from maternal blood and deliver it to the fetus. After birth, the production of adult hemoglobin rapidly increases and fetal hemoglobin production drops off.



Fgure: 1. Thalassemia

In the thalassemia patient, a mutation or deletion of the genes that control globin production occurs. This leads to a decreased production of the corresponding globin chains and an abnormal hemoglobin ratio (α:non-α). This abnormal ratio leads to decreased synthesis of hemoglobin and the expression of thalassemia. The globin that is produced in normal amounts winds up in excess and forms red cell aggregates or inclusions. These aggregates become oxidized and damage the cell membrane, leading either to hemolysis, ineffective erythropoiesis, or both. The quantity and properties of these globin chain aggregates determine the characterstics and severity of the thalassemia.

CLASSIFICATION:

Thalassemia is mainly classified into two types:

- Alpha thalassemia.
- Beta thalassemia.

Alpha thalassemia

Is caused by a deletion or mutation in one or more of the four alpha globin gene copies. The mutation causes a decrease in the production of alpha globin. The more genes that are affected, the less alpha globin is

produced by the body. The four different types of alpha thalassemia are classified according to the number of genes affected and include:

- Silent Carrier State (1 gene affected).
- Alpha Thalassemia Trait (2 genes affected).
- Hemoglobin H Disease (3 genes affected).
- Alpha Thalassemia Major (also called hydropsfetalis, 4 genes affected).

Beta thalassemia

Is caused by mutations in one or both of the beta globin genes. There have been more than 250 mutations identified, but only about 20 are the most common. The severity of the anemia caused by beta thalassemia depends on which mutations are present and whether there is decreased beta globin production (called beta+ thalassemia) or if production is completely absent (called beta0 thalassemia). The different types of beta thalassemia include

- Beta Thalassemia Trait or Beta Thalassemia Minor
- Thalassemia Intermedia.
- Thalassemia Major or Cooley's Anemia.

CAUSES OF THALASSEMIA:

Our body makes three types of blood cells: red blood cells, white blood cells, and platelets (PLATE-lets). Red blood cells contain hemoglobin, an iron-rich protein that carries oxygen from your lungs to all parts of your body. Hemoglobin also carries carbon dioxide (a waste gas) from your body to your lungs, where it's exhaled.

Hemoglobin has two kinds of protein chains: alpha globin and beta globin. If your body doesn't make enough of these protein chains or they're abnormal, red blood cells won't form correctly or carry enough oxygen. Your body won't work well if your red blood cells don't make enough healthy hemoglobin.

Thalassemia is inherited disorders—that is, they're passed from parents to children through genes. People who inherit faulty hemoglobin genes from one parent but normal genes from the other are called carriers. Carriers often have no signs of illness other than mild anemia. However, they can pass the faulty genes on to their children.

People who have moderate to severe forms of thalassemia have inherited faulty genes from both parents.

Alpha Thalassemia-

You need four genes (two from each parent) to make enough alpha globin protein chains. If one or more of the genes is missing, you'll have alpha thalassemia trait or disease. This means that your body doesn't make enough alpha globin protein.

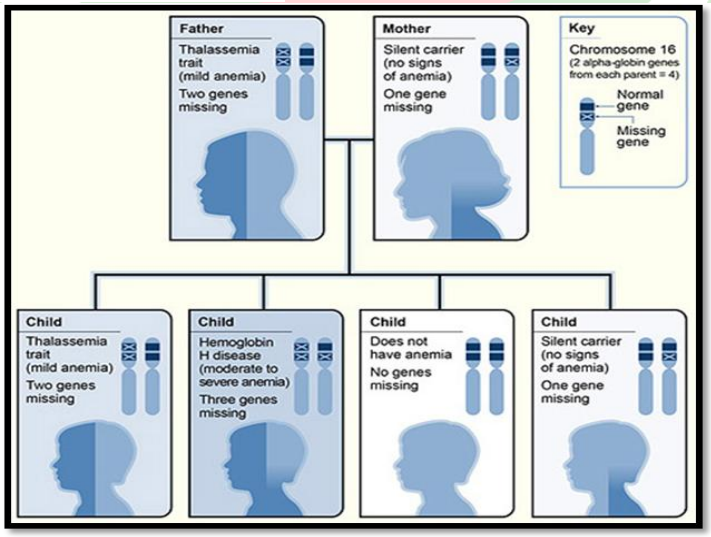


Figure: 2.Example of an Inheritance Pattern for Alpha Thalassemia.

The picture shows one example of how alpha thalassemia is inherited. The alpha globin genes are located on chromosome 16. A child inherits four alpha globin genes (two from each parent). In this example, the father is missing two alpha globin genes and the mother is missing one alpha globin gene. Each child has a 25 percent chance of inheriting two missing genes and two normal genes (thalassemia trait), three missing genes and one normal gene (hemoglobin H disease), four normal genes (no anemia), or one missing gene and three normal genes (silent carrier).

Beta Thalassemias

You need two genes (one from each parent) to make enough beta globin protein chains. If one or both of these genes are altered, you'll have beta thalassemia. This means that your body won't make enough beta globin protein.

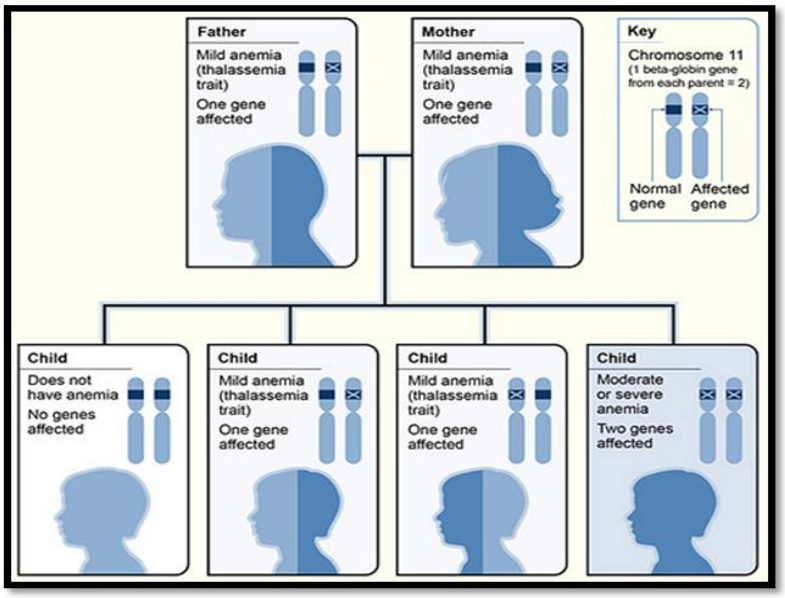


Figure: 3. Example of an Inheritance Pattern for Beta Thalassemia

The picture shows one example of how beta thalassemia is inherited. The beta globin gene is located on chromosome 11. A child inherits two beta globin genes (one from each parent). In this example, each parent has one altered beta globin gene. Each child has a 25 percent chance of inheriting two normal genes (no anemia), a 50 percent chance of inheriting one altered gene and one normal gene (beta thalassemia trait), or a 25 percent chance of inheriting two altered genes (beta thalassemia major).

SIGNS & SYMPTOMS:

Symptoms of thalassemia are mainly two type –

Alpha-thalassemia-

Alpha-thalassemia also has two serious types, which are hemoglobin H disease and hydropsfetalis.

Hemoglobin H disease can cause bone issues. The cheeks, forehead, and jaw may all overgrow. Additionally, hemoglobin H disease can cause:

- Jaundice, which is a yellowing of the skin or the whites of the eyes
- An extremely enlarged spleen
- Malnourishment

Beta-thalassemia-

Beta-thalassemia comes in two serious types, which are thalassemia major, or Cooley's anemia, and thalassemia intermedia.

The symptoms of thalassemia major generally appear before a child's second birthday. The severe anemia related to this condition can be life-threatening. Other signs and symptoms include:

- Fussiness
- Paleness

- Frequent infections
- A poor appetite
- Failure to thrive
- Jaundice, which is a yellowing of the skin or the whites of the eyes
- Enlarged organs

PATHOPHYSIOLOGY:-

Normally, the majority of adult hemoglobin (HbA) is composed of four protein chains, two α and two β globin chains arranged into a heterotetramer. In thalassemia, patients have defects in either the α or β globin chain, causing production of abnormal red blood cells (In sickle-cell disease, the mutation is specific to β globin).

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, two loci encode the β chain, and four loci encode 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-thalassemia. β-Thalassemias are not only common in Africans, but also in Greeks and Italians.

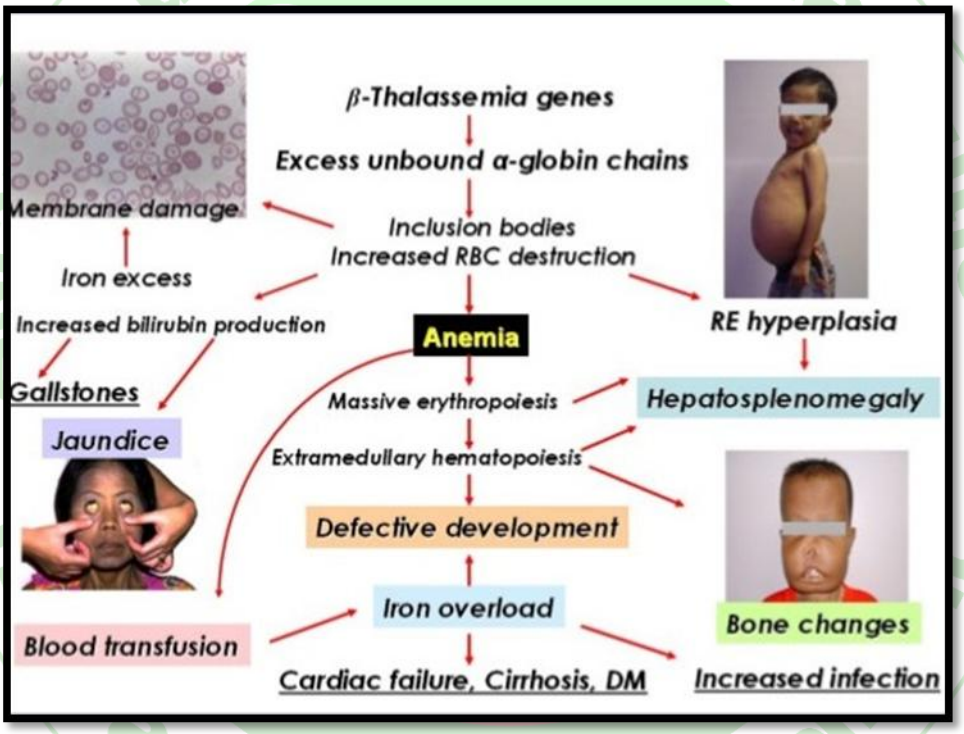


Figure: 4. Pathophysiology of beta thalassemia

DIAGNOSIS

Several laboratory tests may be used to help detect and diagnose thalassemia:

Complete blood count (CBC):

The CBC is an evaluation of the cells in the blood. Among other things, the CBC determines the number of red blood cells present and how much hemoglobin is in them. It evaluates the size and shape of the red blood cells present, reported as the red cell indices.

Blood smear (also called peripheral smear and manual differential):

- Red cells may also:
- Be paler than normal (hypochromic)
- Vary in size and shape (anisocytosis and poikilocytosis)
- Be nucleated (normal, mature RBCs do not have a nucleus)
- Have uneven hemoglobin distribution (producing "target cells" that look like a bull's-eye under the microscope)

Iron studies:

These may include: iron, ferritin, unsaturated iron binding capacity (UIBC), total iron

binding capacity (TIBC), and percent saturation of transferrin. These tests measure different aspects of the body's iron storage and usage. The tests are ordered to help determine whether an iron deficiency is the cause of a person's anemia. One or more of them may also be ordered to help monitor the degree of iron overload in an individual with thalassemia.

Hemoglobinopathy (Hb) evaluation (hemoglobin electrophoresis):

This test assess the type and relative amounts of hemoglobin present in red blood cells. Hemoglobin A (Hb A), composed of both alpha and beta globin, is the type of hemoglobin that normally makes up 95% to 98% of hemoglobin in adults. Hemoglobin A2 (HbA2) is usually 2% to 3% of hemoglobin in adults, while hemoglobin F usually makes up less than 2%.

DNA Analysis:

These tests are used to help confirm mutations in the alpha and beta globin-producing genes. DNA testing is not routinely done but can be used to help diagnose thalassemia and to determine carrier status, if indicated.

TREATMENT:

Treatment depends on the form of condition the patient suffers from. Currently, it is treated with regular blood transfusions and chelation therapy.

Blood transfusion:

Blood transfusion is the main treatment given to patients with major thalassemia. Transfusion is required every 2-3 weeks to supplement RBCs and maintain a haemoglobin level of around 9gm/dL.

Iron chelation therapy:

With repeated blood transfusions, the iron load of the body in thalassemic patients increases. This condition is called iron overload which can create complications and damage other healthy organs including the heart and liver.

Supplements:

Folic acid supplements must be given to enhance the production of healthy RBCs.

Management:

Mild thalassemia:

people with thalassemia traits do not require medical or follow-up care after the initial diagnosis is made.People with β-thalassemia trait should be warned that their condition can be misdiagnosed as the more common iron deficiency anemia.

Blood transfusions:

People with severe thalassemia require medical treatment. A blood transfusion regimen was the first measure effective in prolonging life.

Medications:

Multiple blood transfusions can result in iron overload. The iron overload related to thalassemia may be treated by chelating therapy with the medication defroxamine, deferiprone or deferasirox. These treatments have resulted in improving life expectancy in those with thalassemia major.

Bone marrow transplant:

Bone marrow transplantation may offer the possibility of a cure in young people who have an HLA-matched donor. Success rates have been in the 80–90% range. Mortality from the procedure is about 3%.There are no randomized controlled trials which have tested the safety and efficacy of non-identical donor bone marrow transplantation in persons with β- thalassemia who are dependent on blood transfusion.

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