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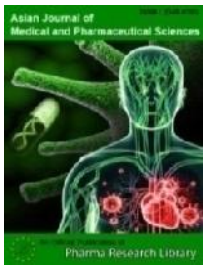

R E V I E W A R T I C L E

An Inherited Genetic Blood Disorder: Thalassemia

D. Pragathi*, Ramesh Dhani, M. Gobinath

Ratnam Institute of Pharmacy, Pidathapolur, Nellore, Andhra Pradesh, India

A B S T R A C T

Thalassemia is an inherited blood disorder characterized by less oxygen-carrying protein (haemoglobin) and fewer red blood cells in the body than normal.It is most common type of haemoglubinopathies transmittedby hereditary. It includes HBA1 and HBA2 genes. Alpha thalassemia involves in decreased alpha-globin production whereas beta thalassemia due to mutations in HBB gene on chromosome. The severity of thalassemia occurs with complications of including iron overload, bone deformities and CVSillness. It results in excessive destruction of RBC which leads to Anemia. Thalassemia leads to cause liver disease and followed by heart failure and even may leads to death.

Keywords: Thalassemia, hemoglubinopathies, hereditary, mutations, anemia.

A R T I C L E I N F O

A U T H O R D E T A I L S

D. Pragathi
Ratnam Institute of Pharmacy,
Pidathapolur, Nellore, Andhra Pradesh, India
Email:desireddypragathi@gmail.com

MS-ID:AJMPS3544

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1. Introduction

Thalassemia is an inherited blood disorder in which the body makes an abnormal form of haemoglobin. Haemoglobin is the protein molecule in red blood cells that carries oxygen. The disorder results in excessive destruction of red blood cells, which leads to anaemia. Anaemia is a condition in which your body doesn't have

enough normal, healthy red blood cells. Thalassemia is inherited, meaning that at least one of your parents must be a carrier of the disease. It's caused by either a genetic mutation or a deletion of certain key gene fragments.

History:

Thalassemia was first recognized in 1925 by a Detroit physician, Cooley and Lee, who described a series of infants who became profoundly anemic and developed splenomegaly and bone change over the first year of life (Cooley and Lee, 1925). George and William (1932), described the pathological changes of the condition for the first time, recognized that many of their patients came from the Mediterranean region, and hence invented the word thalassemia from the Greek words ("thalassa": meaning sea and ("aima": meaning blood)(Whipple and Bradford, 1932).It was only after 1940 that the true genetic character of this disorder was fully appreciated (Weatherall, 2001).

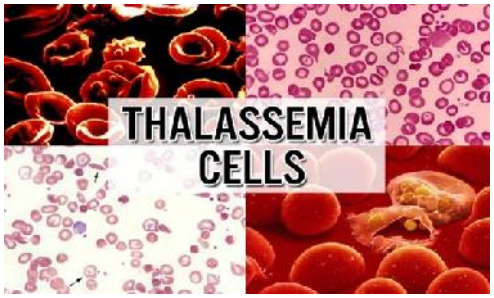

Figure 1

2. Classification of Thalassemia

There are three main types of thalassemia and four subtypes: Beta thalassemia, which includes the subtypes major and intermedia. Alpha thalassemia, which include the subtypes hemoglobin H and hydrops fetalis thalassemia minor. All of these types and subtypes vary in symptoms and severity. The onset may also vary slightly.

Alpha thalassemia:

Alpha thalassemia occurs when the body can't make alpha globin. In order to make alpha globin, you need to have four genes, two from each parent. This type of thalassemia also has two serious types: hemoglobin H disease and hydrops fetalis.

Hemoglobin H develops as when a person is missing three alpha globin genes or experiences changes in these genes. This disease can lead to bone issues. The cheeks, forehead, and jaw may all overgrow. Additionally, hemoglobin H disease can cause: jaundice, an extremely enlarged spleen and malnourishment. Hydrops fetalis is an extremely severe form of thalassemia that occurs before birth. Most individuals with this condition are either stillborn or die shortly after being born. This condition develops when all four alpha globin genes are altered or missing

Thalassemia minor:

People with thalassemia minor don't usually have any symptoms. If they do, it's likely to be minor anemia. The condition is classified as either alpha or beta thalassemia minor. In alpha minor cases, two genes are missing. In beta minor, one gene is missing.The lack of visiblesymptoms can make thalassemia minor difficult to detect. It's important to get tested if one of your parents or a relative has some form of the disease.

Beta thalassemia:

Beta thalassemia occurs when your body can't produce beta globin. Two genes, one from each parent, are inherited to make beta globin. This type of thalassemia comes in two serious subtypes: thalassemia major (Cooley's anemia) and thalassemia intermedia.

Thalassemia major: is the most severe form of beta thalassemia. It develops when beta globin genes are missing. 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

This form of thalassemia is usually so severe that it requires regular blood transfusions.

Thalassemia intermedia are a less severe form. It develops because of alterations in both beta globin genes. People with thalassemia intermedia don't need blood transfusions.

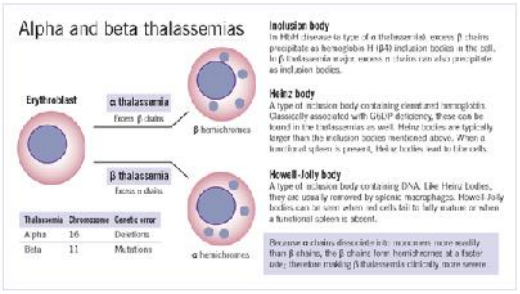

Figure 2

3. Pathophysiology

Alpha-Pathophysiology: The pathophysiology of alpha thalassemia is different to that of beta thalassemia .A deficiency of α chain leads to the production of excess chains or β chains , which form Hb Bart's and Hb H respectively . These soluble tetramers do not precipitate in the bone marrow and hence erythropoiesis is more effective than in β thalassemia. However, Hb H is unstable and precipitates in red cells as they age. The inclusion bodies produced in this way are trapped in the spleen and other parts of the microcirculation leading to shortened red cell survival. Furthermore, both Hb Barts and Hb H have a very high oxygen affinity; because they have no α chains, there is no haem-haem interaction and their oxygen dissociation curves resemble myoglobin (Victor et al., 1999). There are four subtypes of alpha thalassemia that range from mild to severe in their effect on the body (Cohen et al., 2004).

Beta-Pathophysiology:

The molecular defects in β thalassemia result in absent or reduced β chain production .Alpha chain synthesis is

unaffected and hence there is imbalanced globin chain production leading to an excess of α chains. In the absence of their partners, they are unstable and precipitate in the red cell precursors, giving rise to large intracellular inclusions, which interfere with red cell maturation. Hence, there is a variable degree of intramedullary destruction of red cell precursors (i.e. ineffective erythropoiesis). Those red cells that mature and enter the circulation contain α chain inclusion, which interfere with their passage through the microcirculation, particularly in the spleen. These cells, which show a variety of abnormalities of membrane structure and permeability, are prematurely destroyed and thus the anemia of β thalassemia results from both ineffective erythropoiesis and a shortened cell survival. The anemia acts as a stimulus to erythropoietin production and this causes expansion of the bone marrow, which may lead to serious deformities of the skull and long bones. Because the spleen is being constantly bombarded with abnormal red cells, it hypertrophies (Victor et al., 1999).

4. Causes

Around 100,000 newborns are delivered each year with severe forms of thalassemia. It is most common with Mediterranean, South Asian, and African ancestry. Thalassemia occurs when there's an abnormality or mutation in one of the genes involved in hemoglobin production. You inherit this genetic defect from your parents.If only one of your parents is a carrier for thalassemia, you may develop a form of the disease known as thalassemia minor. If this occurs, you probably won't have symptoms, but you'll be a carrier of the disease. Some people with thalassemia minor do develop minor symptoms.If both of your parents are carriers of thalassemia, you have a greater chance of inheriting a more serious form of the disease.

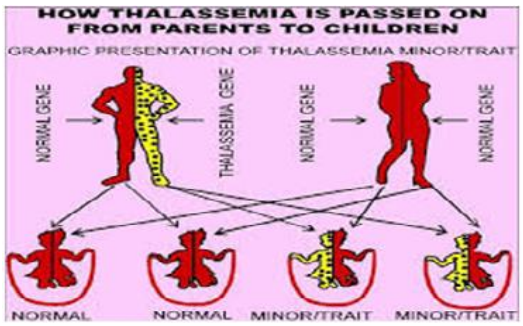

Figure 3

Phenotype	Hb A	Hb Barts	Hb H
Normal	97 – 98%	0	0
Silent Carrier	96 – 98%	0 – 2% (At birth)	0
α Thalassemia	85 – 95%	2 – 8% (At Birth)	< 2%
Hb H Disease	Dec	<10% (At birth)	5 – 40%
Hydrops Fetalis	0	70 – 80% (with 20% Hb Portland)	0 – 20%

Figure 4

According to the Centers for Disease Control and Prevention (CDC), thalassemia is most common in people from Asia, the Middle East, Africa, and Mediterranean countries such as Greece and Turkey.

5. Signs and Symptoms

The symptoms of thalassemia vary depending on the type of thalassemia. Symptoms will not show until the age of 6 months in most infants with beta thalassemia and some types of alpha thalassemia. This is because neonates have a different type of hemoglobin, called foetal hemoglobin.

- ✓ Bone deformities, especially in the face , Dark urine
- ✓ Delayed growth and development, Excessive tiredness and fatigue
- ✓ Yellow or pale skin, Jaundice and pale skin
- ✓ Drowsiness and fatigue, Chest pain
- ✓ Cold hands and feet, Shortness of breath
- ✓ Leg cramps, Rapid heart beat
- ✓ Poor feeding , Delayed growth
- ✓ Headaches, Dizziness and faintness
- ✓ Greater susceptibility to infections,

Not everyone has visible symptoms of thalassemia. Signs of the disorder also tend to show up later in childhood or adolescence.

Skeletal deformities may result as the body tries to produce more bone marrow.

If there is too much iron, the body will try to absorb more iron to compensate. Iron may also accumulate from blood transfusions. Excessive iron can harm the spleen, heart, and liver.

Patients with hemoglobin H are more likely to develop gallstones and an enlarged spleen.

Untreated, the complications of thalassemia can lead to organ failure.

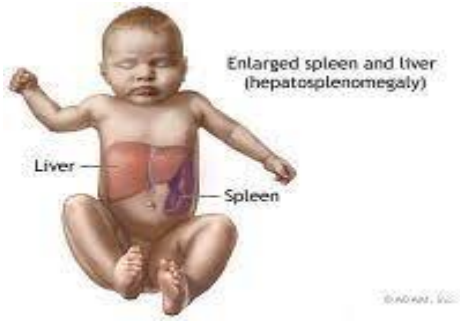

Figure 5

6. Diagnosis

If your doctor is trying to diagnose thalassemia, they'll likely take a blood sample. They'll send this sample to a lab to be tested for anemia and abnormal hemoglobin. A lab technician will also look at the blood under a microscope to see if the red blood cells are oddly shaped. Abnormally shaped red blood cells are a sign of thalassemia. The lab technician may also perform a test known as hemoglobin electrophoresis. This test separates out the different molecules in the red blood cells, allowing them to identify the abnormal type.Depending on the type and severity of the thalassemia, a physical examination might also help your doctor make a diagnosis. For example, a severely

enlarged spleen might suggest to your doctor that you have hemoglobin H disease. Most children with moderate to severe thalassemia show signs and symptoms within their first two years of life. If your doctor suspects your child has thalassemia, he or she may confirm a diagnosis using blood tests. If your child has thalassemia, blood tests may reveal:

- A low level of red blood cells
- Smaller than expected red blood cells
- Pale red blood cells
- Red blood cells that are varied in size and shape
- Red blood cells with uneven hemoglobin distribution, which gives the cells a bull's-eye appearance under the microscope

Blood tests may also be used to:

- Measure the amount of iron in your child's blood
- Evaluate his or her hemoglobin
- Perform DNA analysis to diagnose thalassemia or to determine if a person is carrying mutated hemoglobin genes

Prenatal testing:

Testing can be done before a baby is born to find out if he or she has thalassemia and determine how severe it may be. Tests used to diagnose thalassemia in fetuses include:

Chorionic villussampling. This test is usually done around the 11th week of pregnancy and involves removing a tiny piece of the placenta for evaluation.

Amniocentesis. This test is usually done around the 16th week of pregnancy and involves taking a sample of the fluid that surrounds the fetus.

Assisted reproductive technology:

A form of assisted reproductive technology that combines preimplantation genetic diagnosis with in vitro fertilization may help parents who have thalassemia or who are carriers of a defective hemoglobin gene give birth to healthy babies. The procedure involves retrieving mature eggs and fertilizing them with sperm in a dish in a laboratory. The embryos are tested for the defective genes, and only those without genetic defects are implanted into the uterus.

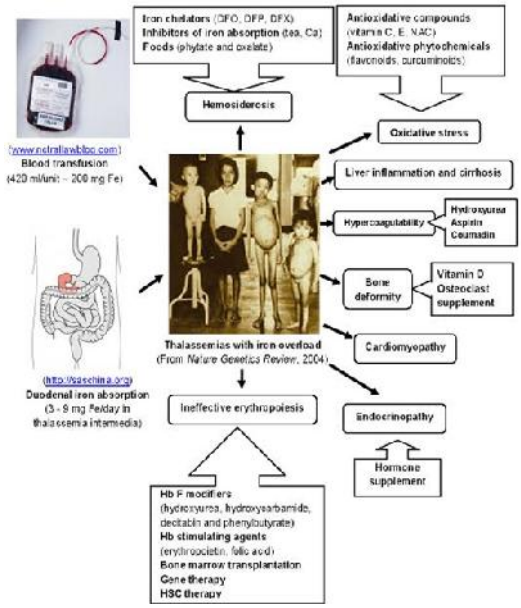

Figure 6

7. Treatment

Treatments for mild thalassemia

Signs and symptoms are usually mild with thalassemia minor and little, if any, treatment is needed. Occasionally, you may need a blood transfusion, particularly after surgery, after having a baby or to help manage thalassemia complications.People with severe beta-thalassemia will need blood transfusions. And because this treatment can cause iron overload, they will also need treatment to remove excess iron. An oral iron chelation medication called deferasirox can help remove the excess iron.

Treatments for moderate to severe thalassemia:

Treatments for moderate to severe thalassemia may include: Frequent blood transfusions. More-severe forms of thalassemia often require frequent blood transfusions, possibly every few weeks. Over time, blood transfusions cause a buildup of iron in your blood, which can damage your heart, liver and other organs. To help your body get rid of the extra iron, you may need to take medications that rid your body of extra iron.

Stem Cell Transplant/Bone marrow Transplant (BmT):

Some children with thalassemia may be cured by a stem cell or bone marrow transplant. Our BMT program delivered the first cure of alpha thalassemia major in the United States. The program participates in national trials and offers options for using either related and unrelated stem cell donors. The Sibling donor Cord Blood Program, the first of its kind in the world, offers a unique treatment option to families. The treatment for thalassemia depends on the type and severity of disease involved. Your doctor will give you a course of treatment that will work best for your particular case.

- Some of the treatments include:
- Blood transfusions
- Bone marrow transplant
- Medications and supplements
- Possible surgery to remove the spleen or gallbladder

Your doctor may instruct you not to take vitamins or supplements containing iron. This is especially true if you need blood transfusions. People who receive blood transfusions receive extra iron that the body can't easily get rid of. Iron can build up in tissues, which can be potentially fatal. If you're receiving a blood transfusion, you may also need chelation therapy. This generally involves receiving an injection of a chemical that binds with iron and other heavy metals. This helps remove extra iron from your body.

Other possible treatments include:

Chelation Therapy The goal of chelation therapy is to maintain the total body iron load in a near-normal range. This requires accurate measurements and expert medical management of each patient's iron load.

Iron measurement:

Children's is one of just two locations in the United States with equipment—known as a ferritometer or SQUId—so advanced it can measure the amount of iron stored in the liver using magnetic fi elds. This non-invasive, painless procedure takes less than 45 minutes. MRI technology is used to evaluate iron overload in the heart and assess cardiac function.

Iron management:

Children's experts help patients to fi nd a chelation regimen suited to their medical needs and personal preferences. We show patients how to administer desferal, a drug that removes excess iron from the body. Our participation in multiple drug trials led to the approval of Exjade, the first oral iron chelation therapy.

Non-Transfusion Treatment:

The vast majority of individuals who have thalassemia do not require regular blood transfusions. Children's specialists can manage these patients' disease through medical and psychosocial interventions.

Lifestyle and home remedies

You can help manage your thalassemia by following your treatment plan and adopting healthy-living habits. The following tips will help:

- ✓ Avoid excess iron. Unless your doctor recommends it, don't take vitamins or other supplements that contain iron.
- ✓ Eat a healthy diet. Eating a balanced diet that contains plenty of nutritious foods can help you feel better and boost your energy. Your doctor also may recommend you take a folic acid supplement to help your body make new red blood cells. Also, to keep your bones healthy, make sure your diet contains adequate calcium and vitamin D. Ask your doctor what the right amounts are for you and whether you need to take a supplement.
- ✓ Avoid infections. Protect yourself from infections with frequent hand-washing and by avoiding sick people. This is especially important if you've had to have your spleen removed. You'll also need an annual flu shot, as well as the meningitis, pneumococcal and hepatitis B vaccines to prevent infections. If you develop a fever or other signs and symptoms of an infection, see your doctor for treatment.

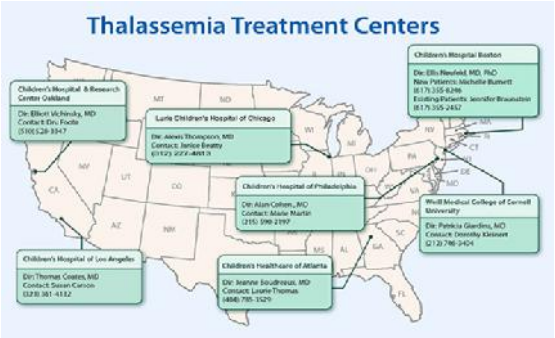

Figure 7

8. Conclusion

The present review concludes that, thalassemia is an inherited blood disorder identified by less oxygen-carrying protein (haemoglobin) and fewer red blood cells in the body than normal. It includes HBA1 and HBA2 genes. The severity of thalassemia occurs with complications of including iron overload, bone deformities and CVS illness. It results in excessive destruction of RBC which leads to Anemia. Thalassemia leads to cause liver disease and followed by heart failure and even may leads to death.

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