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AWARENESS ON THALASEMIA PREVENTION AND ITS TREATMENT IN COMMUNITY PRACTICE-A BRIEF REVIEW

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ABSTRACT

Thalassemia is an inherited blood disorder in which the body makes an abnormal form of hemoglobin. Hemoglobin is the protein molecule in red blood cells that carries oxygen. The disorder results in excessive destruction of red blood cells, which leads to anemia. Anemia is a condition in which your body doesn't have enough normal, healthy red blood cells. In alpha thalassaemia, having one faulty gene will cause little or no effect to a person. 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. Two faulty genes are associated with mild anaemia. Thalassemias are genetic disorders inherited from a person's parents. There are two main types includes alpha thalassemia and beta thalassemia. The severity of alpha and beta thalassemia depends on how many of the four genes for alpha globin or two genes for beta globin are missing. Diagnosis is typically by blood tests including a complete blood count, special hemoglobin tests, and genetic tests is required. It was Treated with regular blood transfusions, iron chelation, and folic acid and Iron chelation may be done with deferoxamine and establishing genetic counseling centers early detection and identification of carriers and marriage between both the carriers we can prevent the disease complications in the community.

KEYWORDS: Red blood cells, Genetic disorders, Hemoglobin, Diseases.

INTRODUCTION

Thalassemia results when mutations affecting the genes involved in Hb biosynthesis lead to decreased Hb production. The clinical phenotype results from both the diminished amount of the particular globin chain as well as from the resultant chain imbalance that occurs because

of normal production of the other globin chain. It might be important to note that the clinical phenotype becomes most apparent at 6-9 months of age; due to the fetal to adult hemoglobin switch that occurs at that age.[1,4]

Thalassemia is an inherited blood disorder in which the body makes an abnormal form of hemoglobin. Hemoglobin is the protein molecule in red blood cells that carries oxygen. The disorder results in excessive destruction of red blood cells, which leads to anemia. Anemia 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 due to either a genetic mutation or a deletion of certain key gene fragments. The two main forms of thalassemia are alpha-thalassemia and beta-thalassemia. In alpha-thalassemia, at least one of the alpha globin genes has a mutation or abnormality. In beta-thalassemia, the beta globin genes are affected. Thalassemias are genetic disorders inherited from a person's parents. There are two main types, alpha thalassemia and beta thalassemia. The severity of alpha and beta thalassemia depends on how many of the four genes for alpha globin or two genes for beta globin are missing.

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. There are two main types of Alpha Thalassemia disease. Alpha Thalassemia Major is a very serious disease in which severe anemia begins even before birth. Pregnant women carrying affected fetuses are themselves at risk for serious pregnancy and delivery complications. Another type of Alpha Thalassemia is Hemoglobin H disease. There are varying degrees of Hemoglobin H disease. 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 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.[5] 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.

Classification of thalassemia

Although there are many types of thalassemic syndromes, each involves decreased production of one globin chain or more, which form the different Hbs normally found in RBCs. In clinical practice, the most important types affect either α- or β-chain synthesis.

The most common forms of α-thalassemia are as follows

- Silent carrier α-thalassemia: The diagnosis cannot be confirmed based on Hb electrophoresis results, which are usually normal in all α-thalassemia traits.
- A-Thalassemia trait: Characterized by mild anemia and low RBC indices.
- Hb H disease: Represents α-thalassemia intermedia, with mildly to moderately severe anemia, splenomegaly, icterus, and abnormal RBC indices.
- A-Thalassemia major: Results in the severe form of homozygous α-thalassemia.

Some of the more common forms of β-thalassemia are as follows

- Silent carrier β-thalassemia: Patients are asymptomatic, except for possible low RBC indices
- B-Thalassemia trait: Patients have mild anemia, abnormal RBC indices and abnormal Hb electrophoresis results with elevated levels of Hb A_2, Hb F, or both
- Thalassemia intermedia: Patients have anemia of intermediate severity
- B-thalassemia associated with β-chain structural variants: The most significant condition in this group of thalassemic syndromes is the Hb E/β thalassemia
- Thalassemia major (Cooley anemia): This condition is characterized by transfusion-dependent anemia, massive splenomegaly, bone deformities, growth retardation and peculiar facies in untreated individuals, 80% of whom die within the first 5 years of life from complications of anemia.[6]

Stages of thalasemia

- Stage I patients: Received fewer than 100 units of packed red blood cells; usually asymptomatic
- Stage II patients: Received 100-400 units of blood; may report slight fatigue

- Stage III patients: Have symptoms ranging from palpitations to CHF.

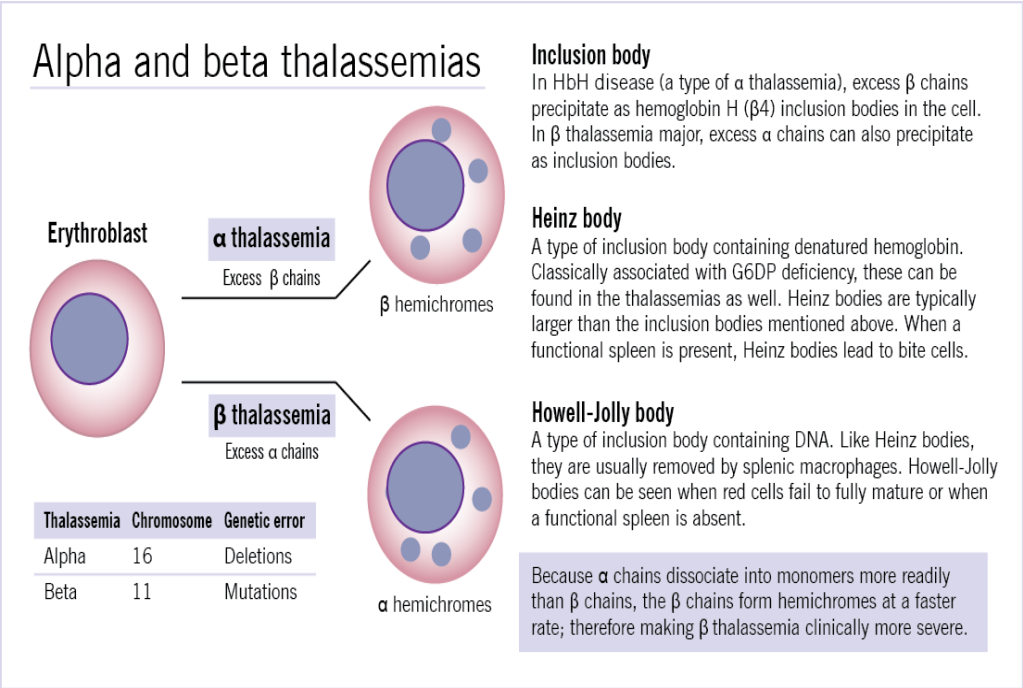

Fig 1: Alpha and beta Thalasemia

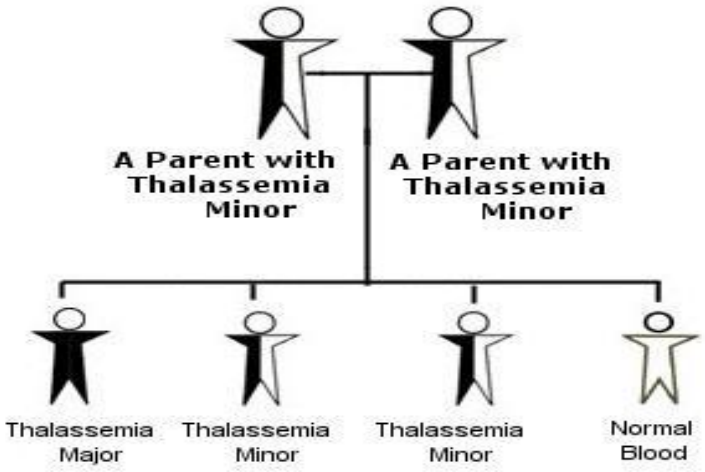

Fig 2: Thalasemia presentation

Alpha Thalassemia

The hemoglobin does not produce enough alpha protein have alpha thalassemia. It is commonly found in Africa, the Middle East, India, Southeast Asia, southern China and occasionally the Mediterranean region.[8]

There are four types of alpha thalassemia that range from mild to severe in their effect on the body.

Silent Carrier State. This condition generally causes no health problems because the lack of alpha protein is so small that the hemoglobin functions normally. It is called “silent carrier” because of how difficult it is to detect. Silent carrier state is “diagnosed” by deduction when an apparently normal individual has a child with hemoglobin H disease or alpha thalassemia trait.

Hemoglobin Constant Spring. This is an unusual form of Silent Carrier state that is caused by a mutation of the alpha globin. It is called Constant Spring after the region of Jamaica in which it was discovered. As in silent carrier state, an individual with this condition usually experiences no related health problems.

Alpha Thalassemia Trait or Mild Alpha Thalassemia. In this condition, the lack of alpha protein is somewhat greater. Patients with this condition have smaller red blood cells and a mild anemia, although many patients do not experience symptoms.

Hemoglobin H Disease

In this condition, the lack of alpha protein is great enough to cause severe anemia and serious health problems such as an enlarged spleen, bone deformities and fatigue. It is named for the abnormal hemoglobin H (created by the remaining beta globin) that destroys red blood cells.

Hemoglobin H-Constant Spring

This condition is more severe than hemoglobin H disease. Individuals with this condition tend to have a more severe anemia and suffer more frequently from enlargement of the spleen and viral infections.[9]

Homozygous Constant Spring

This condition is a variation of hemoglobin H-Constant Spring that occurs when two Constant Spring carriers pass their genes on to their child (as opposed to hemoglobin H Constant Spring, in which one parent is a Constant Spring Carrier and the other a carrier of alpha thalassemia trait). This condition is generally less severe than hemoglobin H Constant Spring and more similar to hemoglobin H disease.

Hydrops Fetalis

In this condition, there are no alpha genes in the individual's DNA, which causes the gamma globins produced by the fetus to form an abnormal hemoglobin called hemoglobin Barts. Most individuals with this condition die before or shortly after birth.

Beta Thalassemia

People whose hemoglobin does not produce enough beta protein have beta thalassemia. It is found in people of Mediterranean descent, such as Italians and Greeks, and is also found in the Arabian Peninsula, Iran, Africa, Southeast Asia and southern China.

There are three types of beta thalassemia that also range from mild to severe in their effect on the body.

Other Forms of Thalassemia

E Beta Thalassemia

Hemoglobin E is one of the most common abnormal hemoglobins. It is usually found in people of Southeast Asian ancestry, such as Cambodians, Vietnamese and Thai. When combined with beta thalassemia, hemoglobin E produces E beta thalassemia, a moderately severe anemia which is similar in symptoms to beta thalassemia intermedia.[10,11]

Sickle Beta Thalassemia

This condition is caused by a combination of beta thalassemia and hemoglobin S, the abnormal hemoglobin found in people with sickle cell disease. It is commonly found in people of Mediterranean ancestry, such as Italians, Greeks and Turks.

Types of Thalassemia

The type of thalassemia you have depends on the number of gene mutations you inherit from your parents and which part of the hemoglobin molecule is affected by the mutations.The more mutated genes, the more severe your thalassemia. Hemoglobin molecules are made of alpha and beta parts that can be affected by mutations.[10]

Alpha-thalassemia

Four genes are involved in making the alpha hemoglobin chain.

1 mutated gene, you'll have no signs or symptoms of thalassemia. But you are a carrier of the disease and can pass it on to your children.

- **2 mutated genes,** your thalassemia signs and symptoms will be mild. This condition may be called alpha-thalassemia trait.
- **3 mutated genes,** your signs and symptoms will be moderate to severe.
- **4 mutated genes.** This type is rare. Affected fetuses have severe anemia and usually are stillborn. Babies born with this condition often die shortly after birth or require lifelong transfusion therapy. In rare cases, a child born with this condition may be treated with transfusions and a stem cell transplant, which is also called a bone marrow transplant.[12]

Causes

Both α- and β-thalassemias are often inherited in an autosomal recessive manner. Cases of dominantly inherited α- and β-thalassemias have been reported, the first of which was in an Irish family with two deletions of 4 and 11 bp in exon 3 interrupted by an insertion of 5 bp in the β-globin gene. For the autosomal recessive forms of the disease, both parents must be carriers for a child to be affected. If both parents carry a hemoglobinopathy trait, the risk is 25% for each pregnancy for an affected child. Genetic counseling and genetic testing are recommended for families who carry a thalassemia trait. Thalassemia occurs when there's an abnormality or mutation in one of the genes involved in hemoglobin production.

Diagnosis

The diagnosis of thalassemia is made through studies such as bone marrow examination, hemoglobin electrophoresis, and iron count. The CBC count and peripheral blood film examination results are usually sufficient to suspect the diagnosis. Hb evaluation confirms the diagnosis in β-thalassemia, Hb H disease, and Hb E/β thalassemia.

Laboratory studies

- CBC count
- Hb electrophoresis
- Peripheral blood smear
- Iron studies (ie, levels of serum iron, serum ferritin)
- Complete RBC phenotype
- Hepatitis screen
- Folic acid level
- level of urinary excretion of iron after deferoxamine challenge
- HLA typing before initiation of blood transfusion therapy
- Renal function tests during chelation therapy

Imaging studies

- Skeletal survey: Reveals classic bony changes in patients who are not regularly transfused
- Chest radiography: To evaluate cardiac size and shape.
- MRI or CT scanning of affected areas: To diagnose complications (eg, bony deformities, compression fractures).
- R2 MRI: For noninvasive measurement of liver and cardiac iron overload and to monitor response to iron chelation therapy (eg, FerriScan).
- T2* MRI: Could evaluate both liver and cardiac iron load simultaneously [2]
- Echocardiography: To monitor cardiac function.

Etiology

- **Mutations fall into two classes**
  - B0 refers to mutations that cause no beta globulin to be produced
  - B+ describes mutations that result in a diminished but not absent quantity of beta globulin. The severity of these mutations can vary depending on the amount of normal beta globulin that is produced.

- Depending the class of mutation present and the gene dosage (i.e. heterozygous or homozygous) patients can present with differing severity of disease
  - Beta thalassemia major: refers to a severe clinical phenotype that occurs when patients are homozygous or compound heterozygous for more severe beta chain mutations (e.g. severe B+/B+ mutations, B+/B0, B0/B0)
  - Beta thalassemia intermedia: An in between clinical phenotype with heterogenous genetic mutations that still allow for some Beta chain production (e.g. B+/B0, B+/B+). Some rare cases also exist in which both beta and alpha mutations coexist.
  - Beta thalassemia minor/ thalassemia trait: a mild clinical phenotype when one normal copy of the beta globulin gene is present (e.g. B+/B, B0/B).

Risk factors

The risk Factors of thalassemia include

- **Family history of thalassemia.** Thalassemia is passed from parents to children through mutated hemoglobin genes.
- **Certain ancestry.** Thalassemia occurs most often in African-Americans and in people of Mediterranean and Southeast Asian ancestry.

EPIDEMIOLOGY

- Approximately 7% of the global population is a carrier for Haemoglobin disorders
- A carrier of a pathological Hb gene encounters no health problems
- Between 300,000 – 500,000 children are born annually with a severe haemoglobin disorder
- About 80% of affected children are born in middle and low income countries
- About 70% are born with sickle cell and the rest with thalassaemia disorders
- 50 – 80% of children with sickle cell anaemia and 50,000 – 100,000 children with β-thalassaemia major die each year in low and middle income countries.
- There is great heterogeneity of these mutants genes of Chinese in different regions in China and South East Asia.
- Carrier status of α - Thalassemia for Chinese range from 2 - 7.6% of general population in areas studied.[13]

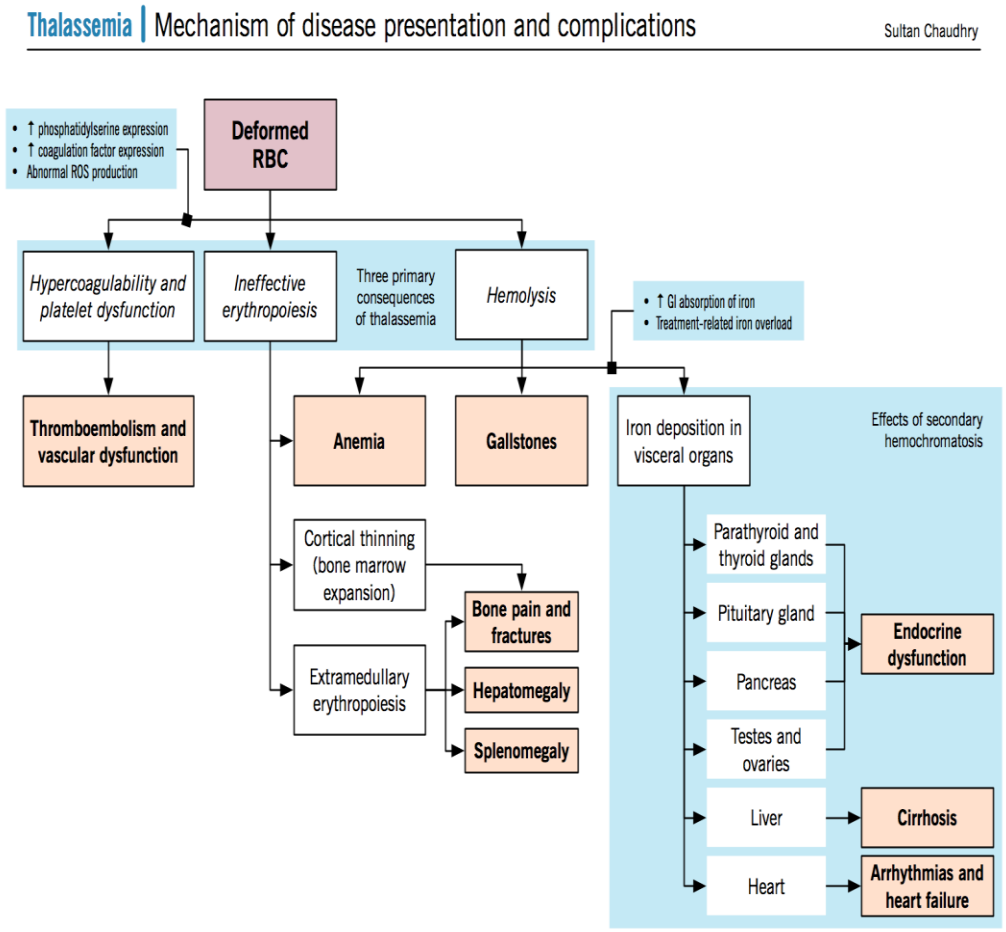

Fig 3: Mechanism of Thalasemia and its complications

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. The thalassemias are classified according to which chain of the hemoglobin molecule is affected. In α-thalassemias, production of the α globin chain is affected, while in β-thalassemia, production of the β globin chain is affected.[14]

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.

Alpha-thalassemias

The α-thalassemias involve the genes HBA1 and HBA2, inherited in a Mendelian recessive fashion. It is also connected to the deletion of the 16p chromosome. αThalassemias result in decreased alpha-globin production, therefore fewer alpha-globin chains are produced, resulting in an excess of β chains in adults and excess γ chains in newborns.

Beta-thalassemia

Beta thalassemias are due to mutations in the *HBB gene* on chromosome 11, also inherited in an autosomal, recessive fashion. The severity of the disease depends on the nature of the mutation and on the presence of mutations in one or both alleles.[15] Mutated alleles are called β^{+} when partial function is conserved (either the protein has a reduced function, or it functions normally but is produced in reduced quantity) or β^{o}, when no functioning protein is produced.

Delta-thalassemia

As well as alpha and beta chains present in hemoglobin, about 3% of adult hemoglobin is made of alpha and delta chains. Just as with beta thalassemia, mutations that affect the ability of this gene to produce delta chains can occur.

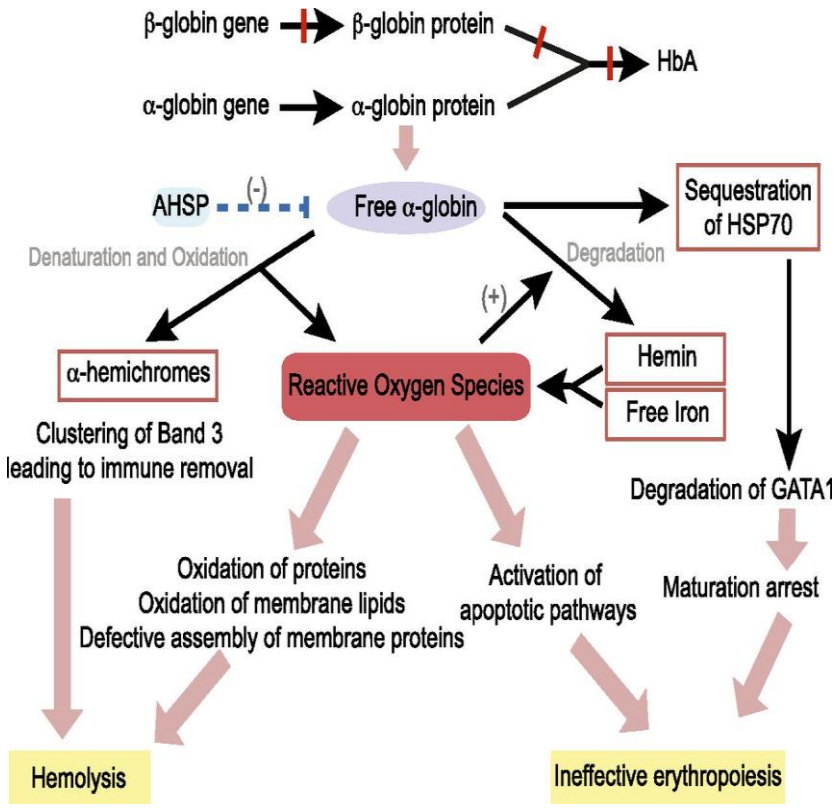

Fig 3: Thalassemia Pathophysiology

Symptoms of thalassemia

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

Alpha-thalassemia

- Fatigue
- Weakness
- Pale or yellowish skin
- Facial bone deformities

- Slow growth
- Abdominal swelling
- Dark urine
- jaundice, which is a yellowing of the skin or the whites of the eyes
- an extremely enlarged spleen
- malnourishment
- surgery

Pharmacotherapy for Thalasemia

- Antipyretics, analgesics (eg, acetaminophen)
- Antihistamines (eg, diphenhydramine)
- Chelating agents (eg, deferoxamine, deferasirox)
- Corticosteroids (eg, hydrocortisone)
- Antibacterial combinations (eg, TMP/SMX, gentamicin, penicillin V)
- Vitamins (eg, ascorbic acid, alpha-tocopherol, folic acid)
- a bone marrow transplant (BMT)
- medications remove the spleen or gallbladder and supplements
- possible
- Vaccines (eg, polyvalent pneumococcal; 7-valent pneumococcal conjugated;
- *H.*influenza.type B; meningitis group A, C, Y, and W-135)
- Antineoplastics (eg, hydroxyurea)
- Growth hormone (eg, somatropin)

Transfusions

- Regular blood transfusions to ensure non-anemic states and prevent some of the disease complications (Target Hb 90-100 g/L)
- Leukodepletion techniques are used to ensure less alloimmunization and non-hemolytic transfusion reactions.
- Testing for viruses is done to reduce transfusion transmitted infections

Iron chelation

- **Deferoxamine/deferiprone** work by binding serum iron and clearing it via the urine.
- Deferiprone has been shown to improve cardiac functioning (left ventricular ejection fraction; LVEF) in patients with thalassemia major.

Endocrine therapy

- Administration of the deficient hormones (sex hormones and thyroid hormones)
- Use of fertility agents to induce spermatogenesis and achievement of pregnancy
- Osteoclast inhibitors (bisphosphonates) to prevent osteopenia and osteoporosis.

Splenectomy and cholecystectomy

- Splenectomies often assist with reducing transfusion requirements
- Cholecystectomies are often required to the presence of bilirubin stones in the gallbladder.

Possible complications of thalassemia include

- **Iron overload.** People with thalassemia can get too much iron in their bodies, either from the disease or from frequent blood transfusions. Too much iron can result in damage to your heart, liver and endocrine system.
- **Infection.** People with thalassemia have an increased risk of infection. This is especially true if you've had your spleen removed.

In cases of severe thalassemia, the following complications can occur:

- **Bone deformities**

Thalassemia can make your bone marrow expand, which causes your bones to widen. This can result in abnormal bone structure, especially in your face and skull. Bone marrow expansion also makes bones thin and brittle, increasing the chance of broken bones.

- **Enlarged spleen (splenomegaly)**

The spleen helps your body fight infection and filter unwanted material, such as old or damaged blood cells. Thalassemia is often accompanied by the destruction of a large number of red blood cells. This causes your spleen to enlarge and work harder than normal. Splenomegaly can make anemia worse, and it can reduce the life of transfused red blood cells. If your spleen grows too big, your doctor may suggest surgery to remove it (splenectomy).

- **Slowed growth rates**

Anemia can cause a child's growth to slow. And thalassemia may cause a delay in puberty.

- **Heart problems**

Heart problems — such as congestive heart failure and abnormal heart rhythms (arrhythmias) — may be associated with severe thalassemia

Awareness about the Community towards Thalasemia Prevention

- marriage between a carrier (minor) and a normal person
- marriage between two carriers (minors)
- carrier detection and premarital screening
- Genetic counseling

Genetic counseling, plays the most important part in thalassemia prevention program. Genetic counseling is given to individuals and in groups for the same type of thalassaemia as well. Moreover pregnant (minor) women having similar carrier partners are counseled for chronic villous sampling (CVS) in order to reduce the birth of thalassaemia major babies.

Extended Family Screening

The control of thalassaemia is possible by screening of general population for carrier status and by prenatal diagnosis in couples at risk of having a child with thalassaemia. The parents with thalassaemic child on a regular transfusion are interviewed using our extended screening forms and our results showed that most of them were more willing to share information on their thalassaemic children with relatives and friends.

Prenatal diagnosis

Pregnant Carrier women (having carrier partners) in their first trimester are diagnosed through chrorionic villus sampling, in order to reduce the chances for birth of a thalassaemia major child.

CONCLUSION

It can be prevented through establishing genetic counseling centers in the hospitals and creating awareness about the disease with in the community is needed. early detection and screening of the disease is required. Identification of carrier and marriage between the carrier we can improve the life progress of the people in the community. Regular monitoring of health progregress as well as blood transfusions, bone marrow transfusions medication compliance plays a key role in the disease management.

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