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Review Article
International Journal of Pharmacy and Engineering (IJPE)
ISSN 2320-849X

A Review on Thalassemia

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Abstract:

Thalassemia (Thalassa is Greek for the sea, Haema is Greek for blood) is the name of a group of genetic blood disorders characterized by anemia due to enhanced RBC destruction. Hemoglobin, the oxygen-carrying component of the RBCs consists of two different proteins, an alpha and a beta. If the body doesn't produce enough of either of these two proteins, the RBCs become defective and cannot carry sufficient oxygen.

Keywords: Thalassemia, RBCs.

1 INTRODUCTION

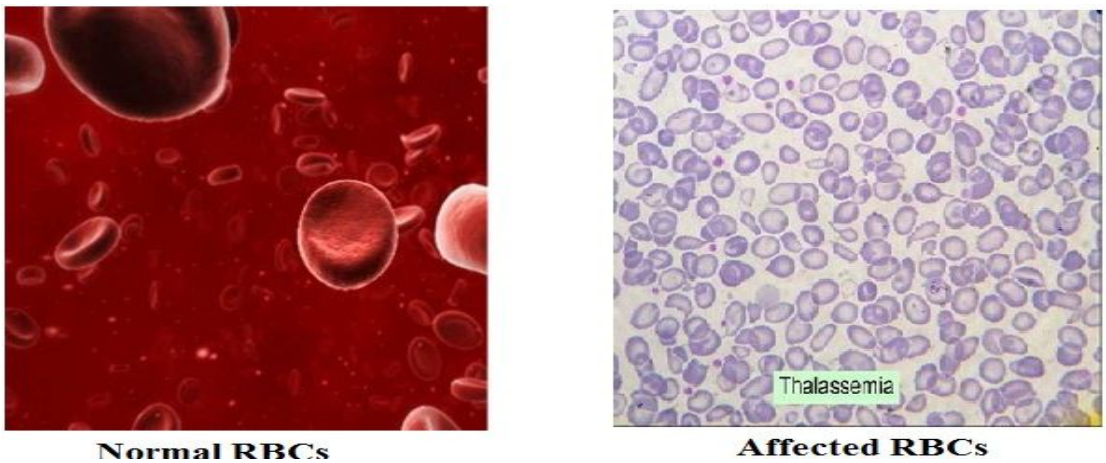

Fig.No.1. Effect on RBCs

The resulting anemia is usually severe with several health problems like enlarged spleen, bone deformities, fatigue and requires regular life-long transfusion, therapy and medical supervision. Thalassemia is an inherited autosomal recessive blood disease. In thalassemia, the genetic defect results in reduced rate of synthesis of one of the globinchains that make up hemoglobin. Deficient synthesis of hemoglobin occurs in thalassemia, a group of hereditary hemolytic anemias. The RBCs are small, pale & short lived. 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.[1]

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. Thalassemia is a common inherited disease in the world. India accounts for 10% of the total world thalassemia population and approximately 1 in 30 in the general population is carrier of the mutated gene. Every year about 15,000 infants are born with haemoglobinopathies in India. Nearly 28 mutations are reported in beta Thalassemia Indian population of which eight accounts for 95% of the cases. Alpha Thalassemia is generally caused by deletions on alpha globin gene. Mutations are specific to population and state specific mutations are reported.[1]

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. Various types of Hb are formed, depending on the types of chains pairing together. Such Hbs exhibit different oxygen-binding characteristics, normally related to the oxygen delivery requirement at different developmental stages in human life**.** 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. Thalassemia produces a deficiency of α or β globin, unlike sickle-cell disease which produces a specific mutant form of β globin. 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 more likely to develop α thalassemias. The thalassemias are inherited disorders of Hb synthesis that result from an alteration in the rate of globin chain production. A decrease in the rate of production of a certain globin chain or chains (α, β, γ, δ) impedes Hb synthesis and creates an imbalance

with the other, normally produced globin chains. Because 2 types of chains (α and non-α) pair with each other at a ratio close to 1:1 to form normal Hbs, an excess of the normally produced type is present and accumulates in the cell as an unstable product, leading to the destruction of the cell. This imbalance is the hallmark of all forms of thalassemia. The reduction varies from a slight decrease to a complete absence of production. The consequences of impaired production of globin chains ultimately result in the deposition of less Hb into each RBC, leading to hypochromasia. The Hb deficiency causes RBCs to be smaller, leading to the classic hypochromic and microcytic picture of thalassemia. However, this does not occur in the silent carrier state, since both Hb level and RBC indices remain normal. Large deletions that may involve the entire β gene, or even extend to delete the neighboring δ gene, have been previously reported. Four new such mutations were recently identified, 3 of these mutations, the deletion has extended to involve the δ gene, resulting in failure to produce any Hb A2. In such cases, the β/δ thalassemia is to be differentiated from the phenotypically similar condition known as hereditary persistence of fetal hemoglobin (HPFH). The importance of differentiating the conditions is reflected in prenatal and newborn screening for hemoglobinopathy. The significant excess of free α chains caused by the deficiency of β chains causes destruction of the RBC precursors in the bone marrow (i.e., ineffective erythropoiesis).[1]

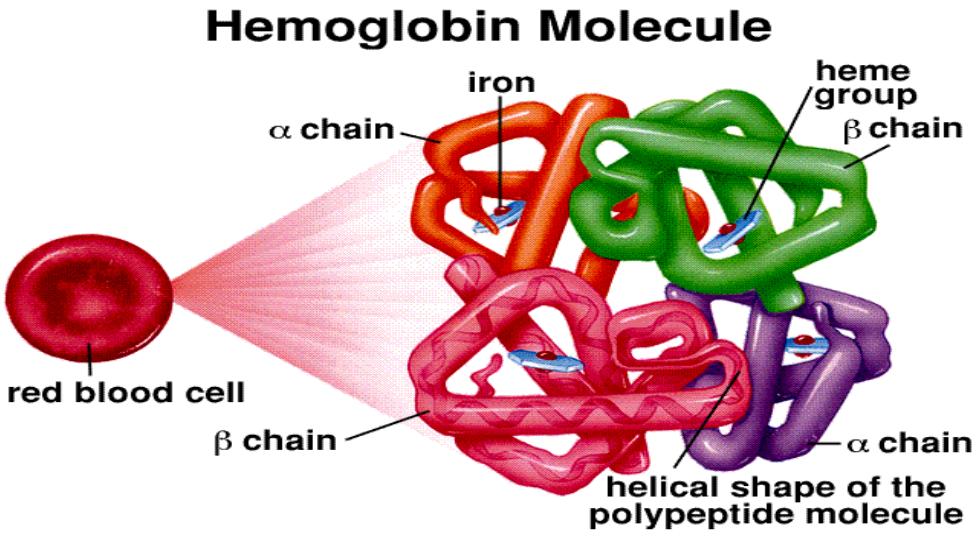

Fig.No.2. Hemoglobin Molecule with Globin Chains

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).[1]

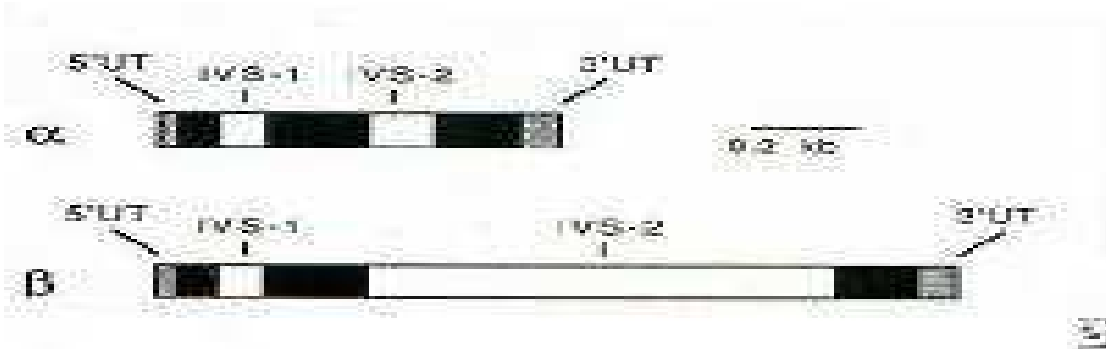

Fig.No.3. α- and β-globin genes(chromosomes 16 and 11, respectively)

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.[2]

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 [2].

TYPES OF THALASSEMIAS

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

INHERITANCE PATTERN FOR ALPHA THALASSEMIA

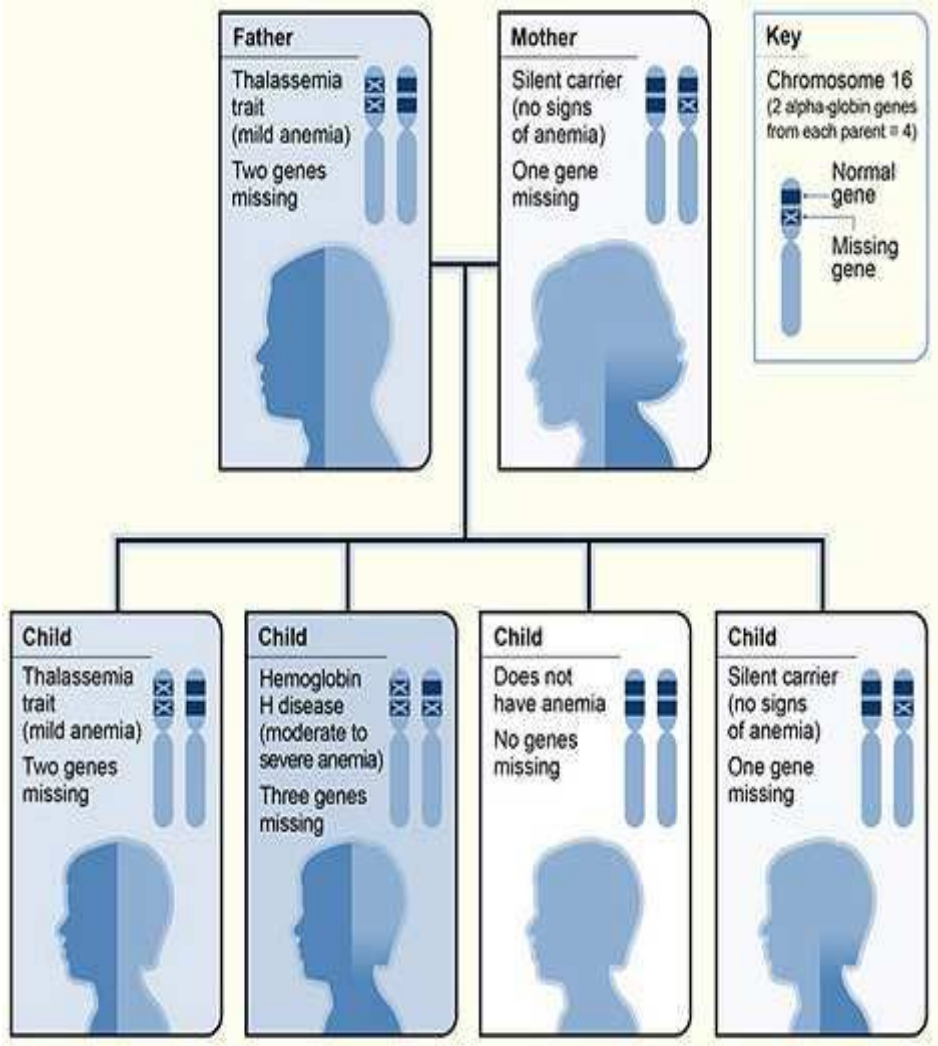

Fig.No.4. Inheritance Pattern for alpha Thalassemia

The fig. shows one example of how alpha thalassemia is inherited. The alpha globin genes are located on chromosome 16 & beta on chromosome 11. 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. Therefore, each child has a 25 percent chance of inheriting two missing genes and two normal genes (thalassemia trait), three missing genes and one normal geneanemia), or one missing gene and three normal genes (silent carrier). A child inherits two beta globin genes—one from each parent.Therefore, 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).

Epidemiology

The worldwide distribution of inherited alpha-thalassemia corresponds to areas of malaria exposure, suggesting a protective role for alpha-thalassemia against the more severe manifestations of malaria. Thus, alpha-thalassemia is common in sub-Saharan Africa, the Mediterranean Basin, the Middle East, South Asia, and Southeast Asia, and different genetic subtypes have variable frequencies in each of these areas. The epidemiology of alpha-thalassemia in the US reflects this global distribution pattern. The most common form of alpha(+) thalassemia seen in the US is due to the -alpha(3.7) deletion, a single alpha-globin gene deletion, and is present in approximately 30% of African Americans. However, even in the homozygous state this disorder will result only in a mild microcytic anemia. The more serious clinical disorders of Hb H and Hb Bart hydrops fetalis syndrome, although found throughout the US today, are more common in the Western US and have dramatically increased in prevalence in the past 2 decades due to increased Asian immigration.

Causes

It is most commonly inherited in a Mendelian recessive fashion. It is also connected to the deletion of the 16p chromosome.

It can also be acquired, under rare circumstances. Due to the low occurrence of alpha-thalassemia, the disease can be mistaken for iron deficiency anemia.

Pathophysiology

α thalassemias 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. The excess β chains form unstable tetramers (called Hemoglobin H or HbH of 4 beta chains) which have abnormal oxygen dissociation curves. The excess γ chains form tetramers which are poor carriers of O_2 since their affinity for O_2 is too high so it is not dissociated in the periphery. Homozygote α^0 thalassemias, where there is lots of γ_4 but no α-globins at all (referred to as Hb Barts), often result in still birth.[3]

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.

Beta-thalassemias can be classified into:

Beta-thalassemia major

Clinical presentation of thalassemia major occurs between 6 and 24 months. Affected infants fail to thrive and become progressively pale. Feeding problems, diarrhea, irritability, recurrent bouts of fever, and progressive enlargement of the abdomen caused by spleen and liver

enlargement may occur. In some developing countries, where due to the lack of resources patients are untreated or poorly transfused, the clinical picture of thalassemia major is characterized by growth

retardation, pallor, jaundice, poor musculature, genu valgum, hepatosplenomegaly,leg ulcers, development of masses fromextramedullary haematopoiesis, and skeletal changes resulting from expansion of the bone marrow. Skeletal changes include deformities in the long bones of the legs and typical craniofacial changes (bossing of the skull,
prominent molar eminence, depression of the bridge of the nose, tendency to a mongoloid slant of the eye, and hypertrophy of the maxillae, which tends to expose the upper teeth).
If a regular transfusion program that maintains a minimum Hb concentration of 9.5 to 10.5 g/dL is initiated, growth and development tends to be normal up to 10 to 12 years . Transfused patients may develop complications related to iron overload. Complications of iron overload in children include growth retardation and failure or delay of sexual maturation. Later iron overload related complications include involvement of the heart (dilated myocardiopathy or rarely arrhythmias), liver (fibrosis and cirrhosis), and endocrine glands (diabetes mellitus, hypogonadism and insufficiency of the parathyroid, thyroid, pituitary, and, less commonly, adrenal glands) . Other complications are hypersplenism,chronic hepatitis (resulting from infection with viruses that cause hepatitis B and/or C), HIV infection, venous
thrombosis, and osteoporosis. The risk for hepatocellularcarcinoma is increased in patients with liver viral infection and iron overload . Compliance with iron chelation therapy (see later) mainly influences frequency and severity of the iron overload-related complications. Individuals who have not been regularly transfused usually die before the second-third decade. Survival of individuals who have been regularly transfused and treated with appropriate chelation extends beyond age of 40 years. Cardiac disease caused by myocardial siderosis is the most important life-limiting complication of iron overload in beta-thalassemia. In fact, cardiac complications are the cause of the deaths in 71% of the patients with beta-thalassemia major .[4].
Beta-thalassemia intermedia
Individuals with thalassemia intermedia present later than thalassemia major, have milder anemia and by definition do not require or only occasionally require transfusion. At the severe end of the clinical spectrum, patients present between the ages of 2 and 6 years and although they are capable of surviving without regular blood transfusion, growth and development are retarded. At the other end of the spectrum are patients who are completely
asymptomatic until adult life with only mild anemia. Hypertrophy of erythroid marrow with the possibility of extramedullary erythropoiesis, a compensatory mechanism of bone marrow to overcome chronic anemia, is common. Its consequences are characteristic deformities of the bone and face, osteoporosis with pathologic fractures of long bones and formation of erythropoietic masses that primarily affect the spleen, liver, lymph nodes, chest and spine. Enlargement of the spleen is also a consequence of its major role in clearing damaged red cells from the bloodstream. Extramedullary erythropoiesis may cause neurological problems such as spinal cord compression with paraplegia and intrathoracic masses. As a result of ineffective erythropoiesis and peripheral hemolysis, thalassemia intermedia patients may develop gallstones, which occur more commonly than in thalassemia major . Patients with thalassemia intermedia frequently develop leg ulcers and have an increased predisposition to thrombosis as compared to thalassemia major, especially if splenectomised. Such events include deep vein thrombosis, portal vein thrombosis, stroke and pulmonary embolism.
Although individuals with thalassemia intermedia are at risk of iron overload secondary to increased intestinal iron absorption, hypogonadism, hypothyroidism and diabetes are not common . Women may have successful spontaneous pregnancies. However, if blood transfusions are necessary during pregnancy, those never or minimally transfused are at risk of developing hemolytic alloantibody and erythrocyte auto antibodies. Intrauterine
growth retardation, despite a regular transfusion regimen, has been reported . Cardiac involvement in thalassemia intermedia results mainly from a high-output state and pulmonary hypertension, while systolic left ventricle function is usually preserved . Pseudoxantoma elasticum, a diffuse connective

tissue disorder with vascular manifestation caused by degeration of the elastic lamina of the arterial wall and calcium deposition, has been described in such patients.[1].

Beta-thalassemia minor

Carriers of thalassemia minor are usually clinically asymptomatic but sometimes have a mild anemia. When both parents are carriers there is a 25% risk at each pregnancy of having children with homozygous thalassemia.

Hemoglobin E Beta Thalassemia:

Hemoglobin E is common abnormal hemoglobin and individuals present a moderately severeanemia which is similar in symptoms to beta thalassemia intermedia **[5].**

Hemoglobin H Disease:

Hemoglobin made from only one gene does not carry oxygen properly. Patients with hemoglobin H disease can suffer from severe anemia [6].

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 [7].

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.

A Public Health Approach

Epidemiology, Surveillance, and Research

The Canters for Disease Control and Prevention's (CDC) Thalassemia Data and Blood Specimen Collection System collects health information that will provide a better understanding of how to reduce or prevent the complications of thalassemia.

Currently, seven Thalassemia Treatment Canters participate in a CDC blood safety and health monitoring program. As part of this program, participants donate blood specimens to be screened for HIV and hepatitis A, B, and C. This repository of tested blood samples allows CDC to facilitate rapid investigation when emerging blood-borne pathogens are identified. In addition, clinical data are collected that can be used to describe the health status and extent of complications of people with thalassemia.

Data collection efforts increase the power to detect emerging infections and provide a more comprehensive view of the clinical characteristics and complications experienced by people with thalassemia nationwide. This knowledge of thalassemia will play a vital role in developing new research ideas and methods to optimize health outcomes for people with this condition.

Current research initiatives focus on several areas:

- The role of comprehensive health care services for thalassemia treatment as a means to prevent complications of the condition.
- The effectiveness of blood safety and surveillance efforts.
- The efficacy and adequacy of prevention and research activities.
- The evaluation of best practices to determine which measures, treatment, and follow-up protocols maximize optimal health outcomes.

Informatics and Infrastructure

CDC supports data collection and analysis for research activities on thalassemia. Because each health care provider may care for a very small number of people with thalassemia in his or her practice, it is necessary to collect data from many providers and settings so that enough data will be available to provide meaningful information.

It is important to design and offer data collection systems that are flexible and minimize the burden of data reporting. To meet this requirement, informatics systems provide the capability for investigators and collaborators to submit data in a variety of formats, including paper forms, electronic submission to

a website, and export of data from third-party software or information systems. Additionally, a sound informatics infrastructure can help to coordinate and align data from multiple sources within a health care setting, such as clinical and laboratory data [8].

Health Education and Health Literacy

As with many of the blood disorders, no cure exists for thalassemia. Therefore, prevention efforts are focused on early identification and the promotion of health behaviours that prevent or lessen complications of this disease. CDC funds and works with our community-based partner, the Cooley's Anemia Foundation (CAF), to support outreach and education activities for people with thalassemia. CDC has collaborated with CAF to develop and translate educational materials for patients and their families and to provide educational materials to community-based providers and service organizations. Focus groups have been used to better understand the issues related to living with thalassemia and have provided useful information for improving education and support programs. This work has resulted in multilingual and culturally appropriate educational materials about the CDC blood safety initiative for more than 1,000 patients and their families. CDC has also sought feedback from the thalassemia community to better understand how to help people live with their treatment regimens.

Other CDC activities include:

Delivering consistent health messages about preventing complications, complying with treatment regimens, and enhancing the quality of life for people with thalassemia and their families.

Participating in outreach activities to identify new patients and provide access to services for underserved populations.

Developing specific materials for nurses to educate families about thalassemia management and its complications [8].

Laboratory Capacity and Support

A priority for CDC is enhancing laboratory research capacity in the community by providing collaborating investigators with services such as subject-matter expertise, technical support, and laboratory analysis. CDC's hematologic laboratories conduct research and provide diagnostic services to people with thalassemia. Currently, CDC is serving as the research and service laboratory for blood safety monitoring by conducting testing for hepatitis A, B, and C and HIV for all participants enrolled in the thalassemia surveillance programs. A bank of blood specimens given regularly by participants is stored for future study of agents or conditions of importance to persons with thalassemia, such as emerging blood-borne infections [9].

DIAGNOSIS

Prior to consideration of transfusion therapy, it is critical to confirm the patient's diagnosis. In addition to complete blood count (CBC), hemoglobin electrophoresis is the first diagnostic test. Fractions of hemoglobin A, A2, F, H, E, and other variants are measured. Hemoglobin analysis by hemoglobin electrophoresis or high performance liquid chromatography is used. Mutations may overlap on the screening test, resulting in incorrect diagnosis or a false negative. Therefore, genetic analysis for both beta-thalassemia and alpha-thalassemia mutations are necessary. In addition, parents and siblings should be screened. Occasionally (up to 20 percent of the time), only a single mutation will be found that is indicative of thalassemia trait. Some such cases result from an autosomal dominant form of thalassemia and others from inheriting a mutation that is not detected by the probes utilized in the DNA testing. Alpha-gene triplication is a common co-factor that may convert a thalassemia trait to a disease or worsen a benign mutation. Testing for co-mutations needs to be requested from the DNA laboratory—otherwise, it will not be performed.

Patients with thalassemia intermedia may have exaggerated anemia due to temporary nutritional deficiencies or infectious complications. It is important to complete a detailed medical history concerning factors that may temporarily lower hemoglobin, including viral illness, marrow-suppressing medication, or exposure to environmental factors such as lead. Nutritional deficiencies in folic acid or iron may exaggerate anemia. Correcting these deficiencies may raise the hemoglobin level enough to obviate the need for transfusion.Therefore, laboratory screening of patients is necessary to rule out other causes of anemia.

Measurements should be taken of the G6PD level, serum ferritin, total iron-binding capacity, serum iron, and red cell folate. A brief therapeutic trial of iron (6 mg/kg/day for four to eight weeks) and folic acid (1 mg/day) are indicated if significant laboratory deficiencies are found.[i]

Hemoglobinopathy (Hb) evaluation:

This test measures the type & relative amounts of hemoglobin present in the RBCs.

DNA analysis:

This test is used to investigate deletions and mutations in the alpha and beta globin producing genes. Family studies can be done to evaluate carrier status and the types of mutations present. Prenatal testing involves taking a sample of amniotic fluid or tissue from the placenta. GeneTech has the best prenatal diagnostic facilities in the country today [10].

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.

Home Treatment:

Iron Multivitamins. Vit. C, increases the amount of iron absorb from food.

Blood Transfusions:

Blood transfusion is the mainstay of care for individuals with thalassemia major and many with intermedia. The purpose of transfusion is twofold: to improve the anemia and to suppress the ineffective erythropoiesis. Chronic transfusions prevent most of the serious growth, skeletal, and neurological complications of thalassemia major. However, once started, the transfusion-related complications become a major source of morbidity. Standards must be developed and maintained to ensure a safe and rational approach to the use of blood transfusions in the management of these rare disorders.

Patients with ß+/ß+ thalassemia; hemoglobin E-ß thalassemia; hemoglobin H disease; and hemoglobin H–Constant Spring often have a thalassemia intermedia phenotype and do not necessarily require chronic transfusion. However, the DNA mutations do not reliably predict the clinical phenotype. ß0/ß+ and even ß0/ß0 may occasionally have a thalassemia intermedia clinical phenotype. The clinical phenotype of thalassemia intermedia patients may change as they age and may require transfusion therapy. Ongoing assessment of transfusion requirements are necessary for both thalassemia major and intermedia.

The decision to start transfusions is based on inability to compensate for the low hemoglobin (signs of increased cardiac effort, tachycardia, sweating, poor feeding, and poor growth), or less commonly, on increasing symptoms of ineffective erythropoiesis (bone changes, massive splenomegaly). The decision to institute chronic transfusion should not be based exclusively on the presence of anemia.

The decision to initiate chronic transfusion therapy requires significant input from the patient, family, and medical team. Anemia alone is not an indication of the need for chronic transfusion. Anemia should be linked with a significant impairment in quality of life or associated morbidities. Factors to consider include: poor growth; inability to maintain daily routines and

activities such as going to school and work; evidence of organ dysfunction; evidence of cardiac disease; pulmonary hypertension; and dysmorphic bone changes.

It may be necessary to initiate a six-month trial of blood transfusions in patients of families whose decision to transfuse is uncertain. After six months, transfusions can be stopped and the patient observed for a brief period of time to give the family and medical team information as to the clinical benefits and psychological impact of the transfusions.

Assessing the need for routine transfusions

The decision to start regular transfusions is clear when the initial hemoglobin level is well below 6 g/dL. To assess a child's need for routine transfusions due to thalassemia, anemia caused by sepsis or viral infection must be ruled out. Assessment may be accomplished by withholding transfusions and monitoring weekly hemoglobin level. If the hemoglobin drops under 7 g/dL on two occasions, two weeks apart, then regular transfusions should be commenced. Patients with a hemoglobin level less than 7 g/dL may sometimes require regular transfusions in the presence of growth impairment, marked skeletal changes, or extramedullary hematopoiesis.

Baseline laboratory tests prior to regular transfusions

An extended red cell phenotype must be obtained to reduce the future probability of developing alloantibodies. If a child has already started transfusions, the red cell antigen genotype can be determined by DNA testing, and at the minimum, should include the C, E, and Kell alleles. Although the hemoglobin level can define a patient's disease type, seldom does it alone determine the need for transfusion. Antibodies to hepatitis B, hepatitis C, and HIV should also be determined. Patients should demonstrate immunity to hepatitis B. The bilirubin, transaminase, and serum ferritin levels should be checked.

Transfusion administration and monitoring

The aim of transfusion therapy is to permit normal growth and activity level and to prevent skeletal changes associated with marrow hyperplasia. Adequate transfusion therapy will also reduce splenomegaly and hypersplenism and decrease absorption of dietary iron[2].

Iron Chelation Therapy:

Iron overload is the major cause of morbidity for thalassemia patients. Even nontransfused patients develop iron overload secondary to increased intestinal absorption of dietary iron. Iron overload is a leading cause of mortality and organ injury. Iron overload occurs very rapidly in patients who are on chronic transfusion programs. Since humans have no mechanism other than sloughing of the mucosa of their gastrointestinal tracts or menstruation to excrete excess iron, patients who are being transfused every three or four weeks gain 0.5 mg/kg per day of iron in excess of natural losses. Patients who are not on a transfusion regimen are also prone to iron overload due to significantly increased intestinal absorption of iron secondary to ineffective erythropoiesis. The only treatment options for removing excess iron are phlebotomy and chelation. While phlebotomy is a very effective way of removing iron, it is not appropriate for patients with thalassemia except after bone marrow transplantation. Thalassemia patients who are not transfusion dependent cannot maintain an adequate hemoglobin level and become symptomatic after phlebotomy. Outpatient exchange transfusion can be used in selected cases to decrease iron intake, but it is not effective by itself in rapidly reducing heavy iron loads and would not be appropriate by itself in the face of cardiac iron loading. The primary treatment for iron overload in thalassemia is chelation, which is described below. Iron is very toxic to tissue. Under normal circumstances, in humans, iron is transported bound to a carrier protein called transferrin. Transferrin transports iron into certain tissues. Because the iron is bound to this protein, other tissues are protected from the toxic effects of free iron. Patients on chronic

transfusion rapidly acquire much more iron than can be bound by transferrin, and free iron levels increase in the blood. This free iron, or so called non-transferrin bound iron, is directly toxic to the heart and other tissues.

There are two goals of iron chelation therapy: the binding of toxic non-transferrin bound iron in the plasma and the removal of iron from the body. Detoxification of excess iron is probably the most important function of chelation therapy. It is clear that certain symptoms of iron overload, such as cardiac arrhythmia and heart failure, can be improved well before local tissue levels of iron have decreased by the continual presence of a chelator in the plasma.

It is useful to think about the toxicity of iron according to the following relation:

Toxicity = [tissue iron] x [patient- and tissue-specific factors] x [time] Generally, time is measured in years. Thus, it takes three to ten years of chronic exposure to high levels of iron before measurable organ dysfunction occurs. Fortunately, this means that there is time to implement treatment strategies to reduce iron loading. However, depending upon the organ, it can take a long time to significantly reduce iron, so the best strategy is acting early and, in fact, trying to prevent significant iron loading from the start. New equipment—such as the quantitative MRI for iron and the ferritometer (SQUID)—has enabled providers to measure the amount of iron in the organs and also look at the relationship between excess iron, time, and patient- and tissue-specific factors. Such factors include transfusion regimen; weekly chelation; differences of transport of iron into various organs; genetic differences in antioxidant defense mechanisms; and disease-specific differences in inflammation and metabolism. It is now clear that there is a tremendous range of variability in end organ toxicity among patients who seemingly have the same amount of tissue iron. From a clinical standpoint, this means that end organ function, as well as tissue iron concentration, must be serially monitored during the management of chronic iron overload. In general, significant iron loading of the liver can be detected after about six months of monthly transfusions, while cardiac loading takes about eight to ten years. The liver loads linearly with time, whereas the heart remains devoid of iron for years. However, once it starts, iron loading of the heart is very rapid. Evidence of liver damage can occur after about four years of transfusions. The onset of cardiac dysfunction is more complex and less well understood. Quantitative cardiac iron, determined by MRI, is reported by T2*. The lower the number, the more the iron. A cardiac T2* greater than 20 ms is not associated with iron-induced cardiac dysfunction. A cardiac T2* between 10 and 20 ms indicates excess iron in the heart and represents a warning for potential cardiac dysfunction. If the T2* is less than 10 ms, the risk of cardiac dysfunction is high, and treatment should be considered emergent. Under full chelation with Deferoxamine, about 50 percent of liver iron can be removed in four to six months. It takes about 17 months to remove half of the heart iron.

Splenectomy:

The use of splenectomy in thalassemia has declined in recent years. This is partly due to a decreased prevalence of hypersplenism in adequately transfused patients. There is also an increased appreciation of the adverse effects of splenectomy on blood coagulation. In general, splenectomy should be avoided unless absolutely indicated [11].

Splenectomy is indicated in the transfusion-dependent patient when hypersplenism increases blood transfusion requirement and prevents adequate control of body iron with chelation therapy. An enlarged spleen—without an associated increase in transfusion requirement—is not necessarily an indication for surgery. Patients with hypersplenism may have moderate to enormous splenomegaly, and some degree of neutropenia or thrombocytopenia may be present.

Annual transfusion volume exceeding 225 to 250 mL/kg per year with packed red blood cells (hematocrit 75 percent) may indicate the presence of hypersplenism. The volume calculation should be corrected if the average hematocrit is less than 75 percent. The possible development of alloantibody should also be ruled out. Splenectomy should be avoided unless there is an inability to maintain iron balance with optimal chelation, or if there are clinically significant complications such as pancytopenia and marked enlargement. Often, hypersplenism develops because of a low pre-transfusion hemoglobin. Increasing the pre-transfusion hemoglobin to between 9.5 and 10 may reverse hypersplenism.

If a decision to perform surgery is made, partial or full splenectomy is the option. Partial splenectomy is a complicated surgery utilized to preserve some splenic function. It should be reserved for infants requiring splenectomy. Full splenectomy can usually be performed by laparoscopic technique. However, open procedure is necessary in cases of marked splenomegaly. The indications for splenectomy in hemoglobin H–Constant Spring patients are different than in beta-thalassemia disorders.

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 [12].

Treatment With Deferoxamine (Desferal)

Deferoxamine (Desferal, DFO) is the most studied iron chelator. It has an excellent safety and efficacy profile and has shown a dramatic effect on increasing survival rates and decreasing morbidity.

Deferoxamine has a poor oral bioavailability. It is administered subcutaneously, intravenously, or occasionally intramuscularly. It has a short half-life, necessitating administration at least eight to twelve hours daily, five to seven days per week. Generally, iron is removed much more efficiently when deferoxamine is infused over a longer period of time. It also can be given intravenously 24 hours per day when indicated. The primary—if not the only—reason deferoxamine is ineffective in some patients is poor compliance.

Deferoxamine is effective in chelating non-transferrin bound iron and can reverse cardiac arrhythmias and left-ventricular dysfunction, although, combination chelation therapy is usually recommended for patients with cardiac dysfunction.

2. Conclusions

Thalassemia is a rare disease in which the appearance of HCC as a complication is mainly the result of recently improved outcomes in developed countries. Preliminary data suggest an incidence of HCC in thalassemia of about 2%. However, since thalassemia is endemic in many under-developed countries where patients are probably not screened for HCC, it is possible that present knowledge of this issue represents only the tip of an iceberg.

Periodic liver Ultrasound HCC screening should probably be considered for thalassemia patients with risk factors for HCC.

Prevention of HCV infection through blood transfusion is nowadays the only known evidence-based means to prevent HCC in thalassemia.

HCC treatment in thalassemia patients should be the same as for non thalassemia HCC patients. Although coexistence of severe co morbidities makes the role of liver transplantation challenging, this

therapeutic possibility should not be precluded for well selected HCC thalassemia patients. Of course, a multidisciplinary effort is needed for management of transplantation patients.
Many of the considerations reported in this review are extrapolated from scanty data that surely lack comprehensive evidence and they are mainly the personal opinion of the author. Multicenter international studies should be performed to strengthen these data.

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