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Research Article

THALASSEMIA

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A B S T R A C T

Thalassemia is the name of a group of genetic blood disorders characterized by anemia due to enhanced red blood cell destruction. Hemoglobin, the oxygen-carrying component of the red blood cells consists of two different proteins, an alpha and a beta. If the body doesn't produce enough of either of these two proteins, the red blood cells become defective and cannot carry sufficient oxygen. 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.

Thalassemias can't be prevented because they're inherited, "inherited" means they are passed on from parents to children. However, these bleeding disorders can be found before birth through prenatal tests. 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 and the cases may increase as it is a hereditary disorder, so, it is important to take into consideration about this disorder as it may prove deadly one. And thus the intensity of this disorder can be lowered by diagnosing and taking proper treatments.

INTRODUCTION

The thalassemias are a group of anemias that result from inherited defects in the production of hemoglobin. The thalassemias are among the most common genetic disorders worldwide, occurring more frequently in the Mediterranean region [1], the Indian subcontinent, Southeast Asia, and West Africa [2]. Ineffective bone marrow erythropoiesis and excessive red blood cell hemolysis together account for the anemia.Since reticulocytes manufacture equimolecular quantities of alpha and beta chains, mature erythrocytes contain essentially equimolecular amounts of each chain [3]. Patients with thalassemia do not produce enough haemoglobin (Hb) A ($\alpha_2\beta_2$) because their cells cannot manufacture either the alpha or beta polypeptide chain of human haemoglobin. Alpha-thalassemia depresses only the production of the alpha chains, and beta-thalassemia depresses only the production of the beta chains. Clinically, both alpha- and beta-thalassemia may occur in the major (homozygous), intermediate, and minor (heterozygous) genetic forms and also can interact with the presence of abnormal hemoglobins in the same individual [4]

To explain the nature of the thalassemia syndromes, it is necessary to outline the interplay of the various polypeptide chains of haemoglobin during normal human development.

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In the first trimester of intrauterine life, zeta, epsilon, alpha, and gamma chains attain significant levels and in various combinations form Hb Gower I ($\zeta_2\epsilon_2$), Hb Gower II ($\alpha_2\epsilon_2$), Hb Portland ($\zeta_2\gamma_2$), and fetalhaemoglobin (HbF) ($\alpha_2\gamma_2$ 136-G and $\alpha_2\gamma_2$ 136-A) (5) Whereas Hb Gower and Hb Portland soon disappear, HbF persists and forms the predominant respiratory pigment during intrauterine life. Before birth, gamma-chain production begins to wane so that after the age of 6 months postpartum, only small amounts of HbF (<2%) can be detected in the blood (6). In early intrauterine life, beta-chain synthesis is maintained at a low level but gradually increases to significant concentrations by the end of the third trimester and continues into neonatal and adult life. The synthesis of delta chains remains at a low level throughout adult life (<3%). Hence during normal development, the synthesis of the embryonic hemoglobins Gower and Portland is succeeded by the synthesis of HbF, which in turn is replaced by the adult hemoglobins, HbA and HbA2Clinically the thalassemia syndromes are heterogeneous due to the many possible mutations affecting the human globin chain loci. These mutations include those of gene deletions, as well as globin chain initiation, translation, and termination [7].

Brief Historical Review

By the beginning of the 20th century, European clinicians had become aware of an anemia syndrome in infancy associated with enlargement of the spleen [8]. In the American literature the first clinical description of thalassemia is attributed to the Detroit pediatriciansThomas B. Cooley and Pearl Lee [9].

The actual term thalassemia was coined by George Whipple [10]. How this term arose remains obscure, although it is reported that early patients were mostly of Mediterranean origin.During the 1960s a genetic basis of the thalassemia diseases was proposed, linking them to unbalanced globin chain synthesis [11].The stage was set for further progress. Simpler methodology was developed that made it possible for routine laboratories to analyse levels of haemoglobin $A_2$and confirm the diagnosis of thalassemia [12]. Other observations on the alterations of haemoglobin patterns inpatients with thalassemia led to the discovery of HbH (β_4) [13] and HbBarts (γ_4) [14], which later became established markers of alpha-thalassemia.

At Johns Hopkins University, David Weatherall and associates labeled reticulocytes of thalassemic patients with radioactive amino acids in vitro and were able to demonstrate that in patients with alpha- and beta-thalassemia, alpha- or beta-chain production was defective because of unbalanced globin chain synthesis [15].At that point, it became necessary to determine whether protein synthesis was abnormal at the level of the structural gene or of globin chain synthesis.

A series of experiments revealed a quantitative or qualitative deficiency of specific messenger RNA in many thalassemia syndromes as well as defects in the translation of the messenger RNA to protein [16]. This latter stage requires ribosomal units that can initiate (promote or enhance), elongate, and terminate the globin chain [17]. Hence a clearer picture of the genetic control of human hemoglobins had emerged. It became clear that several structural loci, i.e., alpha, beta, gamma, and delta, were responsible for the production of their respective globin chains.

Types of Thalassemias

Alpha- Thalassemia

Each human diploid cell contains four copies of the alpha-globin gene, located on chromo-some 16. Whereas alpha-thalassemia is usually caused by one or more deletions of the alpha-globin chain loci, not all alpha-thalassemias are due to gene deletions [17]. Clinically there are four alpha-thalassemia syndromes: silent carrier, alpha-thalassemia trait, HbH disease, and hydropsfetalis syndrome. These occur because of inheritance of molecular mutations affecting the output of one, two, three, or four of the alpha-globin genes. According to written convention, the alpha-thalassemia syndromes can be expressed as α^0 and α^+. In the α^0, no alpha chains are produced. In the α^+, the output of one of the linked pair of alpha-globin genes is defective, and only some alpha chains are produced. Within these general categories of the alpha-thalassemia syndromes, there is considerable genetic and clinical heterogeneity due to the interaction of the many possible mutations directing globin chain synthesis.[18]

Since alpha chains are present in both fetal and adult haemoglobins, a deficiency of alpha-chain synthesis affects haemoglobin production in fetal as well as in adult life. A reduced rate of alpha-chain synthesis in fetal life results in the formation of gamma-chain tetramers (HbBarts). In adult life, a deficiency of alpha chains results in the formation of beta-chain tetramers (HbH) as well as a deficiency in the formation of HbA_2 ($\alpha_2\delta_2$).[18].

The anemia that ensues is also due to shortened red cell survival: beta-chain tetramers (HbH) can precipitate and form inclusion bodies that damage the red cell membrane. Since HbBarts (γ_4) is more stable than HbH (β_4), it does not readily form inclusion bodies. Nevertheless, both HbBarts and HbH show no heme-heme interaction and have high oxygen affinities. Consequently, they are extremely poor oxygen carriers [18].

In response to the oxygen deprivation caused by the anemia, the dyserythropoietic marrow expands, leading to extramedullary erythropoiesis in the bone, liver, and spleen. This erythropoiesis gives rise to skeletal deformities and bony fractures, megaloblasticanemia due to folate deficiency, and hyperuricemia with gout.[18].

Beta- Thalassemia

The beta-gene cluster region resides on chromosome 11. The beta-thalassemias can be divided into several varieties. In β^0 thalassemia, there is a total absence of beta-chain production. In β^+ thalassemia, there is a partial deficiency of beta-chain production. Hypochromia and microcytosis characterize all forms of beta-thalassemia. Because the synthesis of beta chains is almost completely inhibited in thalassemia major, a severe anemia begins at about 3 to 6 months of age, the time when gamma-chain synthesis normally decreases. The anemia produces a stress situation in the bone marrow. This leads to the continuation of HbF synthesis but at a rate far below what is necessary for adequate compensation of the anemia.[18] The HbF produced is unevenly distributed in the red cells and accounts for the anisochromasia. Large numbers of imperfect red cells are destroyed in the bone marrow, giving rise to ineffective erythropoiesis, which is such a prominent feature of the disease. Accelerated apoptosis, the major cause of ineffective erythropoiesis, is caused by excess alpha chain deposited in the erythroid precursors [17].

The haemoglobin pattern in patients with homozygous thalassemia (beta-thalassemia major) consists of a variable increase in HbF, which then accounts for 8% to 90% of the total haemoglobin concentration. The terms *beta-thalassemia intermedia, beta-thalassemia minor*, and beta-thalassemia trait or carrier are used to reflect the decreasing clinical severity of the anemia.[9]

Delta- Thalassemia

In $\delta\beta^+$ thalassemia, an abnormalhaemoglobin, HbLepore, is produced [15].HbLepore has a normal alpha chain combined with a nonalpha chain that consists of the N-terminal residue of the delta chain fused with the C-terminal residue of the beta chain. Many different varieties of HbLepore have been described in which the transition from delta to beta amino acid sequences occurs at different points [15]. Essentially the Leporenonalpha chain is a delta-beta fusion chain. This haemoglobin has little clinical importance yet is of great genetic interest. The occurrence of HbLepore serves to establish the concept of neighboring delta- and beta-chain loci on the same gene, with the delta locus leading the beta locus [18]. Individuals who carry such genes have up to 25% HbLepore in their circulation as well as increased levels of HbF (5%–70%). The Leporehaemoglobins have been found sporadically in most racial groups and rarely give rise to significant anemia [18].

Haemoglobin E Beta-Thalassemia

Compound heterozygotes for HbE and beta-thalassemia are extremely common in Thailand and Southeast Asia. Patients with these disorders can suffer from a moderate to severe anemia and require regular transfusion [15]. Today HbE thalassemia is considered one of the most common and most important hemoglobinopathies in the world. This condition is becoming more prevalent in the USA as a result of Asian immigration[15].

Clinical Features of Severe Thalassemic Syndromes

Infants and children affected with thalassemia have pallor, poor development, and abdominal enlargementHaaemoglobin electrophoretic patterns show a variable quantity of HbA2(0%_6%). due to a combination of ineffective erythropoiesis, excessive peripheral red blood cell haemolysis, and progressive splenomegaly The latter causes an increase in plasma volume and a decrease in total red cell mass. The reticulocyte count is usually <1%. The red cells are microcyticwith marked anisochromasia. The bone marrow shows marked erythroid hyperplasia, and the serum ferritin level is elevated. For diagnostic purposes the parents' hematologic status should be evaluated.

In children and young adults, radiologic abnormalities include thinning of the long bones with sun-ray appearance and dilation of the marrow cavities. The skull has a “hair-on-end” appearance because of widening in the diploic space. Patients with thalassemia have enlarged maxillary sinuses and tend to have a maxillary overbite. The face gradually assumes a “mongoloid” appearance. Such changes promote infections in the ears, nose, and throat. Because of chronic anemia and iron overload, endocrinopathies such as hypopituitarism, hypothyroidism, hypoparathyroidism, diabetes mellitus, cardiomyopathy, and testicular or ovarian failure become common as the child with thalassemia grows older [9]

Thalassemia can be regarded as a chronic hypercoagulablestate, Venous and arterial thromboembolic phenomena tend to occur more frequently in thalassemic patients who have undergone splenectomy. Furthermore, such patients may develop progressive pulmonary arterial disease due to platelet thrombi in the pulmonary circulation. The reasons for the pro-coagulant effect in thalassemia remain obscure, although it has been proposed that erythrocyte membrane abnormalities such as phosphatidylserine formation on the surface of thalassemic red cells activate the coagulation system. [9]

Therapeutic Measures

Chronic anemia in thalassemic patients is managed with blood transfusion, iron chelation, and splenectomy in cases of hypersplenism. In recent years several different transfusion regimens have been proposed to promote normal growth, decrease cardiac load, and lessen iron deposition in tissues. More recently, clinical experience suggests that such criteria may be achieved by maintaining a haemoglobin level of 9 to 10 g/dL throughout life. The transfusions are given once a month using washed, filtered, or frozen red cells in order to reduce noxious reactions to foreign cells and plasma proteins. A few medical centers specializing in the treatment of thalassemic patients use younger red cell populations, “neocytes,” for transfusion with the aim of reducing transfusion frequency. [11]

Prevention

In countries with a high incidence of thalassemia, it is vitally important to offer prospective genetic counseling and to warn carriers about the risks of intramarriage. To date, attempts at this approach have been relatively unsuccessful. Hence, considerable efforts have been directed towards prenatal diagnosis programs. As carrier states of the thalassemias are readily identifiable, affected fetuses can be diagnosed. Recent efforts have been directed to early diagnosis by fetal DNA analysis carried out on amniotic fluid cells or by chorionic villus sampling. Also, the development of oligonucleotide probes to detect individual mutations has markedly increased the accuracy rate of prenatal diagnosis. The harvesting of fetal cells from the maternal circulation is being explored for this purpose [9]

Diagnosis

Doctors diagnose thalassemias using blood tests, including a Complete blood count (CBC) and special haemoglobin tests. Thalassemia lowers your RBC count and causes RBCs to be smaller than usual. It will give the doctor an evaluation of the size and shape of the RBCs present, also called the red cell indices. These include the mean corpuscular volume (MCV), a measurement of the size of the RBCs. [12]

Haemoglobinopathy (Hb) evaluation: This test measures the type & relative amounts of haemoglobin present in the RBCs. [12]

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[12]

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. [12]

Home Treatment: Iron Multivitamins. Vit. C, increases the amount of iron absorb from food. [12]

Blood Transfusions: RBCs live for only about 120 days. So, one may need repeated transfusions to maintain a supply of healthyRBCs[12]

Iron Chelation Therapy: Because the haemoglobin in RBCs is an iron-rich protein, regular blood transfusions can lead to a buildup of iron in the blood. This condition is called iron overload. It damages the liver, heart, and other parts of the body. To prevent this damage, iron chelation therapy is needed to remove excess iron from the body. Two medicines are used for iron chelation therapy. Deferoxamine is a liquid medicine that's given slowly under the skin, usually with a small portable pump used overnight. This therapy takes time and can be mildly painful. Side effects include loss of vision and hearing. Deferasirox is a pill taken once a day. Side effects include headache, nausea, vomiting, diarrhea, joint pain, and fatigue. [9]

Splenectomy: When the spleen becomes too active and starts to destroy the RBCs, transfusions become less effective. Then it become necessary to take the spleen out called "Splenectomy". [12]

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. [12]

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]

CONCLUSION

From the above survey of information it can be well known that the Thalassemia is a dangerous disorder which is spreading worldwide and this is a casual thing to be considered that about 10% people in India are affected by it and the cases may increase as it is a hereditary disorder. 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. So, it is important to take into consideration about this disorder as it may prove deadly one. And thus the intensity of this disorder can be lowered by diagnosing and taking proper treatments such as-

- Blood Transfusions
- Iron Chelation Therapy
- Folic Acid Supplements
- Blood and Marrow Stem Cell Transplant
- Certain Medications as Deferoxamine&Deferasirox

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