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Review Article

MANAGEMENT OF THALASSEMIA

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ABSTRACT
The thalassemias are a heterogeneous group of genetic disorders characterized by decreased or absent production of one or more globin chains that make up a hemoglobin molecule. Each hemoglobin molecule is composed of four globin chains; normally two from thea family and two from the b family of globin chains. Each hemoglobin molecule also has a heme group containing iron. The thalassemia is broadly categorized according to the globin chain that is defective. The common signs and symptoms of thalassemic diseases include pale skin, retarded growth and puberty, anemia, enlarged spleen, and increased susceptibility to infections. The present work summarizes etiology, complication issues, management and prognosis of thalassemias.
Keywords: Thalassemia, Etiology, Complication, Management

INTRODUCTION

Thalassemia (Mediterranean anemia) is an inherited blood disorder characterized by less hemoglobin and fewer red blood cells in your body than normal[1]. It is a pediatric inherited disease caused by genetic disorder. There is an absence or reduction in the production of hemoglobin. There are two type of thalassemia –alpha or beta-depending on which globin chain is affected by a genetic mutation or deletion.[2] Thalassemia is characterized by severe anemia, growth retardation, skeletal disturbances, and iron overload, cardiac and endocrine abnormalities which cut short the life of the affected patients.[3]

Etiology

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 Hemoglobinopathies in India. Early 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.[4-5] Thalassemia belongs to the category of genetic disorders which are expressed when both genes in the pair are affected. Such inheritance is called autosomal recessive inheritance. Genes responsible for hemoglobin synthesis are defective (mutated) or are missing altogether in the disease. Hundreds of mutations have been reported on globin genes causing thalassemia.

Epidemiology

The true Prevalence has estimated 5-7 % of the population worldwide carries clinically significant hemoglobin mutations. β thalassemia is most commonly found in the populations of Southern Europe, Southeast Asia, Africa, and India. α thalassemia is widespread in Africa, Mediterranean populations, the Middle East, and Southeast Asia.[6]

Pathophysiology

Role of Oxidant Injury

These ROSs are generated in increased amounts in thalassemic red blood cells (RBCs) because the deposition of excess unmatched globin chains (α in β thalassemia and β in α thalassemia) contains free iron, nonheme iron, and hemi chromes. These compounds can generate ROS by several mechanisms, including action as a Fenton reagent. More recent data showed that in comparison with children with iron deficiency anemia, children with β thalassemia had elevated plasma levels of conjugated dienes and thiobarbituric acid-reactive substances. These are markers of lipid oxidation. The levels of RBC protective antioxidant enzymes, superoxide dismutase, and glutathione peroxidase were increased[7], implying that ongoing intra-erythrocytic oxidant injury led to induction of antioxidant mechanisms. Iron compounds that could generate reactive oxygen species have been identified on β thalassemia intermedia RBC membranes. Thus, membrane bound free iron, non heme iron, and heme compounds (mainly hemichromes and methemoglobin) are very much increased, particularly in the RBCs of splenectomized Subjects.[8] This finding suggests that the spleen normally removes the most heavily iron-loaded and thus severely damaged RBCs. The level of the RBC antioxidant, reduced glutathione, is reduced by almost 70 %[8-9]. To summarize: there is evidence of oxidant injury to RBC hemoglobin, membrane proteins, and lipids; the possible sources of generation of ROS in thalassemic RBC have been identified; antioxidant RBC enzyme activity is increased; and the RBC level of the antioxidant glutathione is much reduced.

Role of Cellular pathophysiology

The basic defect in all types of thalassemia is imbalanced globin chain synthesis. However, the consequences of accumulation of the excessive globin chains in the various types of thalassemia are different. In β thalassemia, excessive α chains, unable to form Hb tetramers, precipitate in the RBC precursors and, in one way or another, produce most of the manifestations encountered in all of the β thalassemia syndromes; this is not the situation in α thalassemia. The excessive chains in α thalassemia are γ chains earlier in life and β chains later in life. Because such chains are relatively soluble, they are able to form homotetramers that, although relatively unstable, nevertheless remain viable and able to produce soluble Hb molecules such as Hb Bart (4 γ chains) and Hb H (4 β chains). These basic differences in the 2 main types of thalassemia are responsible for the major differences

in their clinical manifestations and severity. α chains that accumulate in the RBC precursors are insoluble, precipitate in the cell, interact with the membrane (causing significant damage), and interfere with cell division. This leads to excessive intramedullary destruction of the RBC precursors. In addition, the surviving cells that arrive in the peripheral blood with intracellular inclusion bodies (excess chains) are subject to hemolysis; this means that both hemolysis and ineffective erythropoiesis cause anemia in the person with β thalassemia. The ability of some RBCs to maintain the production of γ chains, which are capable of pairing with some of the excessive α chains to produce Hb F, is advantageous. Binding some of the excess a chains undoubtedly reduces the symptoms of the disease and provides additional Hb with oxygen-carrying ability. Furthermore, increased production of Hb F, in response to severe anemia, adds another mechanism to protect the RBCs in persons with β thalassemia. The elevated Hb F level increases oxygen affinity, leading to hypoxia, which, together with the profound anemia, stimulates the production of erythropoietin. As a result, severe expansion of the ineffective erythroid mass leads to severe bone expansion and deformities. Both iron absorption and metabolic rate increase, adding more symptoms to the clinical and laboratory manifestations of the disease. The large numbers of abnormal RBCs processed by the spleen, together with its hematopoietic response to the anemia if untreated, results in massive splenomegaly, leading to manifestations of hypersplenism. If the chronic anemia in these patients is corrected with regular blood transfusions, the severe expansion of the ineffective marrow is reversed. Adding a second source of iron would theoretically result in more harm to the patient. However, this is not the case because iron absorption is regulated by 2 major factors: ineffective erythropoiesis and iron status in the patient. Ineffective erythropoiesis results in increased absorption of iron because of down regulation of the HAMP gene, which produces a liver hormone called hepcidin. Hepcidin regulates dietary iron absorption, plasma iron concentration, and tissue iron distribution and is the major regulator of iron. It acts by causing degradation of its receptor, the cellular iron exporter ferroportin. When ferroportin is degraded, it decreases iron flow into the plasma from the gut, from macrophages, and from hepatocytes, leading to a low plasma iron concentration. In severe hepcidin deficiency, iron absorption is increased and macrophages are usually iron depleted, such as is observed in patients with thalassemia intermedia.[10-11]

Complication

Complications are still common and include heart disease (heart failure and arrhythmias), chronic liver hepatitis, which can evolve in cirrhosis and, rarely, in hepatocellular carcinoma, endocrine problems (hypogonadism, hypothyroidism, diabetes, hypoparathyroidism), stunted growth, osteoporosis, thrombophilia and pseudo xanthomaelasticum. The incidence of complications is decreasing by the blood transfusion of new oral iron chelators and imaging methods. In addition, therapy for several complications is available.[12]

Types of Thalassemia

Hemoglobin, the oxygen-carrying protein in red blood cells, is made up of two chains, an alpha chain and a beta chain. These two chains are made from specific genes we inherit from our parents. When these specific genes are not working properly, hemoglobin production is affected. There are two major types of thalassemia.

Alpha Thalassemia

A child inherits four genes, two from each parent, that control the production of hemoglobin alpha chain. Alpha thalassemia occurs when one or more of these genes fail to work properly. The severity of alpha thalassemia depends on the number of defective genes:

Silent Carrier

With one defective gene, the body still makes hemoglobin. Therefore, the person will not feel any symptoms and can lead a normal and healthy life.

Alpha Thalassemia Minor

The loss of two normal genes causes the red blood cells to be smaller than usual. Except for possible mild anemia, patients remain in good health.

Hemoglobin H Disease

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

Alpha Thalassemia Major

With all four genes failing to produce the alpha chain, the body has a significant loss of hemoglobin which results in a severe form of anemia.

Beta Thalassemia

Unlike the alpha chain, the production of hemoglobin beta chain is determined bytwo genes, one from each parent. The severity of beta thalassemia depends on whether one or both of the genes fail to work properly. Beta Thalassemia Minor occurs when one beta gene is defective. People with beta thalassemia minor have smaller red blood cells, but no major health problems. Beta Thalassemia Major (also known as Cooley's anemia) is the most severe form of thalassemia in which both beta genes fail. The body makes little or no beta chain which results in severe anemia.[13]

Diet in Thalassemia

The cause of anemia in thalassemia patients is different from those who suffer from iron-deficiency anemia. Therefore, eating iron-rich foods or taking iron supplements will not treat thalassemia. On the contrary, as described above, those who go through blood transfusion as a treatment for severe thalassemia can have excess iron level that is harmful to the body because of the excess iron in the body, [13] there is a higher risk of oxidative damage.[14] As a result, thalassemia patients are advised to avoid iron-rich foods, such as spinach, beef, pork, lamb, liver, and dried beans.[13]

Treatment

Treatments for thalassemia depend on the type and severity of the disorder. People who are carriers or who have alpha or beta thalassemia trait have mild or no symptoms. They need little or no treatment. There are three standard treatments for moderate and severe forms of thalassemia. These include blood transfusions, iron chelation therapy, and folic acid supplements. Other treatments have been developed or are being tested, but they're used much less often.

Blood Transfusions

Transfusions of red blood cells are the main treatment for the people who have moderate or severe thalassemia. This treatment gives you healthy red blood cells with normal hemoglobin. Red blood cells live only for about 120 days. So, need to repeated transfusions to maintain a supply of healthy red blood cells.[15]

Chelation therapy

Recently patients with thalassemia major who received only transfusion therapy could not survive beyond adolescence, largely because of cardiac complications caused by iron toxicity. The introduction of chelating agents capable of removing excessive iron from the body has dramatically increased life expectancy. When administered in conjunction with blood transfusion regimens, chelation can delay the onset of cardiac disease and, in some patients, even prevent its occurrence. Several chelating agents have been tested, and, although many failed, one particular agent was proven effective and safe. DFO is a complex hydroxylamine with high affinity for iron; it targets the labile pool, the non transferrin-bound iron (free pool), and the ferritin generated from reticulo endothelial iron[16]. Patients receiving chelation therapy have been demonstrated to have some degree of vitamin C deficiency. This deficiency has been attributed, in part, to increased catabolism. Administration of vitamin C increases the urinary excretion of iron and raises both serum iron and ferritin levels; this is probably related to the fact that vitamin C slows down the conversion of ferritin to hemosiderin, leading to the availability of more chelatable iron. Conversely, vitamin C enhances iron-mediated peroxidation of membrane lipids, leading to significant toxicity, mostly cardiac dysfunction in patients who are receiving large doses of vitamin C supplementation in addition to chelation therapy. Vitamin E deficiency: Vitamin E deficiency has been reported in patients with severe thalassemia. Some of the hemolysis in this population was attributed to peroxidation of the RBC membrane lipids by an iron-mediated free radical effect. As an antioxidant, vitamin E is expected to decrease cell toxicity.[17]

Splenectomy

When the spleen becomes too active and starts to destroy the RBCs, transfusions become less effective. Then it became necessary to take the spleen out called "Splenectomy".[18]

Folic acid deficiency

This deficiency is a common complication in patients with thalassemia, mainly because of the extreme demand associated with the severe expansion of the marrow. Other causes, such as poor absorption and intake, can also contribute to folate deficiency.

Hematopoietic stem cell transplantation (HSCT)

HSCT is recommended only for selected patients; it is the only known curative treatment for thalassemia. Poor outcome after HSCT correlates with the presence of hepatomegaly and portal fibrosis and with ineffective chelation prior to transplant. The event-free survival rate for patients who have all 3 features is 59 %, compared to 90 % for those who lack all 3. Platelet transfusion refractoriness has been an issue in patients undergoing HSCT, mainly due to frequent blood transfusions. Human leukocyte antigen (HLA)-matched platelets were reported to be effective in 74 % of cases compared with only 26 % with random donor platelets.[17]

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 Hemoglobinopathies 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. Future perspectives include gene therapy research with co-regulation of globin transgene expression and silencing the mutant genes, and homologous DNA recombination techniques. Proteomic studies will extend the level of analysis of nucleic acids to the final gene expression products and their functional networks. New personalized therapies will hopefully emerge from the pharmacogenomic analysis of individual biologic variation in drug metabolism and efficacy.

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