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Iron Overload and Chelation Strategies Effects on Cardiac Arrhythmia in Beta-Thalassemia Major

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ABSTRACT

Thalassemia is the name of a category of genetically inherited blood disorder passed down through families where the body produces an irregular type of hemoglobin, the protein that carries oxygen in red blood cells. This contributes to premature red blood cell death, leading to anemia. In addition, iron overload causes a threat to vital organs such as the liver and heart. Similarly, organs are affected by iron overload differently. Regular transfusion diagnosis, chelation therapy, bone marrow transplantation and medicine to reduce the accumulation of transfusion iron approximately 1.5% of the world's population are β-thalassemia heterozygotes; there is a high prevalence of populations from the Mediterranean basin to the Pacific Islands across the Middle East, the Indian Subcontinent, Southeast Asia, and Melanesia. Iron chelation agents solve problems of excess iron.

INTRODUCTION

Thalassemia is genetic blood disorder that decreases the development of functional haemoglobin. Haemoglobin exists to serve as the oxygen-carrying component of red blood cells. It is an aspect of the red blood cells that carry oxygen. It is made up of two proteins, each part comprises of alpha and beta. If the body does not deliver enough of any of these two proteins, blood cells do not develop normally and can-not carry sufficient oxygen; the outcome is anemia that starts and persists in early infancy. Thalassemia is a hereditary disease, which means that at least one parent must be a carrier of the disorder. It is caused either by a genetic disorder or by the deletion of certain main segments of the gene.

Alpha Thalassemia is caused by the deletion of the alpha-globin gene which results in the production of alpha-globin chains being reduced or not present. The alpha-globin gene has 4 alleles, and the severity of the disorder varies based on the number of allele deletion, from moderate to severe [1]. The most extreme type in which no alpha globins and excess gamma chains are formed (present during the fetal period) and leads to fetal hydrops (a condition that occurs when large amounts of fluid buildup in a baby's tissues and organs causing extreme swelling). The mildest form is one allele deletion and is mostly clinically silent.

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Beta Thalassemia is the mutation from the beta-globin gene results to the beta-thalassemia. It is divided into three groups, depending on the beta-gene mutation zygosity (degree of similarity of the alleles for a trait in an organism). A heterozygous mutation (beta-plus thalassemia) leads to a mild beta-thalassemia resulting in beta chains. It is generally mild and asymptomatic. A homozygous Beta-globin mutation (non-zero thalassemia) gene causes beta-thalassemia major, resulting in a total absence of beta chains. It medically characterizes as jaundice, growth retardation, hepatosplenomegaly, endocrine abnormalities and severe anemia requiring lifelong transfusions of blood [2]. Beta-thalassemia intermedia with mild to moderate clinical symptoms are the disorder between these two forms. This is known as Major Thalassemia. It used to be called Colley anemia. In general, babies born with two irregular beta hemoglobin genes are stable at delivery, but when fetal hemoglobin (Hb-gamma) fails and is substituted with adult Hb, illness begins to manifest after 6 months of life. It has similarity with a beta-thalassemia phenotype, as thalassemia individuals are commonly found to have HbE in this area.

Types of Thalassemia

Is a hereditary autosomal recessive disorder. Those who don't generate enough protein chains for alpha-globin have alpha thalassemia. Four genes together (HBA1 and HBA2) are expressed as the alpha-globin 2 on each strand of chromosome 16. A patient with alpha thalassemia disorder usually has a single or both defective alpha-globin genes. It's said that a person with one anomalous alpha-globin gene is a silent carrier of alpha thalassemia. A disorder where one of the four alpha-globin genes us absent or damaged, usually does not cause any health issues because, there is such a small loss of an alpha-globin protein that no anemia occurs. The presence of it can be identified through the unique DNA diagnosis. Silent carrier status is "diagnosed" whenever an infant with hemoglobin H disease is minor alpha thalassemia has a normal individual. It is said that a person with two irregular alpha globin genes has a characteristic of alpha thalassemia. The two defective genes may be on the same chromosome or the pair's separate chromosome.

LITERATURE REVIEW

Thalassemia is usually inherited in an autosomal recessive manner. Hemoglobin, which passes oxygen from the lungs to other areas of the body; Hemoglobin consists of two different protein chains, known as alpha and beta globin’s. Two genes, one on each chromosome 11, make beta-globin. Patients with an irregular beta-globin gene have a trait of beta-thalassemia (also known as beta-thalassemia minor). On a global level it is in, Far East, Middle East, India, Central Asia, South China and the Mediterranean as well as in countries along the north of Africa and South America.

In almost every nation on the planet, including Northern Europe, where thalassemia was historically absent, migration and marriages between different ethnicities induced thalassemia in humans. Beta-thalassemia has been reported to be around 1.5 per cent of the world's population (80-90 million people) carriers, with about 60,000 serving as symptoms born globally, the overwhelming majority in the developing countries in particular. The internationally estimated average annual frequency of symptomatic people is 1 in 100,000. Beta-thalassemia with irregular Hb or structural Hb form with thalassemic characteristics has been the most common combination within the region of South East Asia with a carrier level of about 50%.

Role of Hepcidin

The deficiency of hepcidin hormone allows a disproportionate level of iron absorption and raise to a situation such as iron overload in blood streams. The most affected organ form this iron overload condition is human liver because of the keen absorption of non-transferring bound iron by hepatocytes. Apart from the dietary iron absorption in beta thalassemia major there are dominant causes of iron overload. Patients with regular blood transfusion the concentration of hepcidin is higher notably to the non-transfused patients. However this high level of hepcidin concentration decline in multiple transfusions as the influence of each increasing transfusion decreases. A decrease in hepcidin level results in significant level of intestinal absorption of iron. In some of the cases non transfused blood patient, iron concentration have indistinguishable iron absorption with transfused blood patients. Nevertheless this iron is deposited in non-transfused thalassemia patients happened to be in hepatocytes, however in transfused cases the occurred in macrophages.

Specific amounts of hepcidin absorption in intermediate and major thalassemia result in various cellular concentrations of iron. As a result of such a disparity in the supply in cellular iron, serum ferritin rates were significantly lowers in non-transfusion patients, and don’t affect the liver of the non-transfused patients. A particular form of cellular iron deposition is significant, since various kind of cells show change in resistance to iron toxicity.

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Treatment

The standard treatment choices focus on thalassemia's severity. People with mild form often need little or no medication, while individuals with moderate to serious thalassemia can need regular blood transfusions, iron chelation therapy (treatments to remove excess iron from the body) and/or supplementation of folic acid.

Thalassemia is autosomal recessive, simply means both parents need to be affected with or carrier for the disease to pass it on to the next generation. It is caused by mutations of the Hb genes, resulting in alpha or beta chains being under-produced or not present. More than 200 mutations are known as the causes of thalassemias. Alpha thalassemia and beta-thalassemia are caused by deletion of alpha-globin and beta-globin genes respectively caused by a point mutation on chromosome 11 in the splice site and promoter regions of the beta-globin gene.

Some patients with thalassemia disorder are found to have an incidence count when mild microcytic anemia is observed in their standard blood samples. Thalassemia, iron deficiency, chronic sideroblastic anemia and lead poisoning (also known as plumbism) responsible for microcytic anemia. Some of these etiologies may be omitted by the Mean Corpuscular Volume (MCV), the red blood cell distribution width (RDW), and the patient background.

Metabolism of thalassemia and iron

Erythropoiesis (from Greek 'erythro' meaning "red" and 'poiesis' meaning "to make") and iron (Fe) metabolism are closely related. The hormone that regulates the absorption of iron is hepcidin, synthesized in the liver. Hepcidin synthesis is regulated by transferrin saturation, concentration iron, inflammation and erythropoiesis demand. Several erythroid factors affect hepcidin development, e.g. growth differentiation factor (GDF-15) and erythroferrone (Erfe). Increased IE (interleukin), anemia, and inflammation lead to a rise in GDF-15 development leading to suppression of hepcidin. This, in turn, results in increased absorption of Fe from the intestine. High intestine absorption of Fe leads to an increase in iron overload, especially in individuals with NTDT (Non-transfusion-dependent Thalassemia) and contributes to the transfusion overload of Fe in individuals with TDT (Transfusion-dependent Thalassemia).

Intracellular iron trafficking and transportation

Ferroportin, recognized as a cellulose iron exporter. Ferroportin protein is established on the enterocyte basolateral membrane (into the blood capillary) certain cells, such as reticuloendothelial macrophages. Transfer of iron the form of ferrous (Fe^{2+}) and ferric (Fe^{3+}) is carried out by ferroportin, transferrin bindings, and ferroxidases are suspected to play an important role in iron exports. Hephaestin is thought to be the active ferroxidase in intestinal enterocytes, while ceruloplasmin, either circulating or multi copper-ferroxidase linked to GPI, performs this activity in other cells. The transferrin-transferrin receptor system delivers the iron to peripheral tissues. This is inhibited with endocytosis and dispersed by the transferrin receptor errireductase Steap family protein, following acidification of the endosome iron. It is reported that Ferroportin has transcriptionally regulated in Enterocytes and Macrophages, transcriptionally regulated in and translationally controlled by IRP (iron-response element) present in ferroportin mRNA. The intracellular level of iron influences the IRE-IRP cycle. In low iron conditions, the activated IRPs bind to the IRE of ferroportin mRNA resulting in the suppression of translation. Furthermore, ferroportin is monitored by a master hormone, hepcidin, at a post-translation stage. This mRNA is produced using an optional, upstream gene promoter and the mRNA has the same open reading frame. The mRNA (known as FPN1B) would not comprise IRE in the 5'-UTR and is therefore not reviewed by an iron deficit. The comparative expression of these two signals is widely believed to be regulated during erythropoiesis to make sure the iron was transported from the cells early in the differentiation but retained in the cells later in the differentiation when heme synthesis starts and iron demand begins to its peak.

Iron overload in beta-thalassemia

In the extreme form of beta-thalassemia, standard transfusion of blood is needed to reduce the chances of anaemia. RBC (red blood cells) count strengthened by monthly blood transfusions, hemolysis and increase absorption of gastrointestinal iron contributes to iron overload, and its Cardiac stiffness is the leading cause of death in patients with thalassemia related to transfusion. 1-2 mg of iron is excreted from the human body in a day, whereas a transfused red blood cell unit contains about 200 mg of iron. In absence of any iron chelation therapy, an individual getting 25 blood units a year requires 5 g of iron each year. Iron toxicity is highly harmful to all cells in

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the body can cause severe and permanent organ failure, such as liver disease, diabetes, cardiac failure and testosterone deficiency. The iron surcharge in the bloodstream can be measured using, urinary iron excretion, hepatic iron content, serum ferritin and TIBC (Total Iron Binding Capacity) levels. The iron toxicity threshold values are concentration of, serum ferritin >2500 ng/mL, urinary iron discharge >20 mg/day, concentration of liver iron more than 440 mmol/g and transferrin congestion >75%. Estimating the concentration of hepatic iron by MRI (magnetic resonance imaging) is a widely used method in beta-thalassemia major to assess overburden of iron. Iron over-burden has additionally been seen in patients with NTDT (non-transfusion-subordinate thalassemia). In Beta-thalassemia with histidine to aspartic acid (H63D) experience mutation in carriers patients, iron overload at codon 63 of the HFE gene which indicates that the H63D mutation can influence the absorption of iron. Iron deficiency increases the risk of hepatitis, (swollen liver), fibrosis, and cirrhosis or irreversible damage to the liver due to scarring iron deficiency also raises the chance of abnormal heart rhythms/arrhythmias, or, and cardiac obstruction.

DISCUSSION

There are approximately 20 mammalian bone morphogenetic proteins (BMPs), among which BMP2, BMP4, BMP5, BMP6, BMP7 and BMP9 can cause Hamp expression. Studies have shown that the most important among all of the bone morphogenetic proteins (BMPs) is BMP6 which is an important factor for the regulation of the hepcidin. To activate Smad1/5/8 phosphorylation, it attaches to the BMP receptor (BMPR), and the latter translocates to the nucleus together with Smad4 and binds to the Hamp promoter to promote Hamp transcription. BMPR type I expresses only Activin-Like Kinase 2/3 mammals [3]. Unlike many other members of the BMP protein family, the BMP signaling pathway is the essential iron-mediated regulator of hepcidin as BMP6 is sensitive to iron concentrations. BMP6 is developed in non-parenchymal liver cells and stimulated by iron; its expression is relative to the amount of hepatic iron. Furthermore, neutralizing the BMP6 antibody may reduce hepcidin expression and cause serum iron concentrations to increase in mice.

The amount of iron in the human body is calculated through dietary consumption of iron, not through iron excretion. The removal of iron from the human body is handled at a very small rate. The fecal secretion of iron is equivalent to the consumption of iron by diet, and zero in the case of iron by transfusion. However, several cases such as blood transfusion in beta thalassemia in which suppress in production of hepcidin may lead to an overload of iron. Most significant medical issues can be induced by unintended exposures, such as cardiac arrhythmia, liver cirrhosis. As a consequence, the absorption of iron is closely controlled to avoid cell damage. Toxification of iron mainly occurs where it is stored i.e, liver. Biliary iron excretion which estimated a significant amount of excess iron extraction thought the bile and remaining to be processes for the reuse of hemoglobin synthesis. Urinary iron excretion a usual routine excretion of iron in the urine is a large proportion of the overall daily iron depletion.

Since low hepcidin levels are associated with greater Fe absorption in the intestine; inhibitors of hepcidin in thalassemia patients may boost the iron load. Small peptides such as Mini-hepcidins mimetic that are necessary to induce hepcidin actions; hence, serum iron levels decrease and iron overload improves. By using these mini-hepcidins, iron overload and damage to the erythroid cells are significantly reduced. Apo-transferrin administration can decrease labile plasma iron concentrations, leading to a normalization of RBC survival and increased production of Hb. The protein also exists during the early phases of a clinical study. As the Hamp negative regulator, 17b estradiol (E2) therapy reduced Hamp expression in cell lines HuH7 and Hep G2, which could be blocked by ICI 182780, an estrogen receptor antagonist.

Hepcidin, the hormone which regulates the accumulation of absorption of iron and its abnormal transportation are causes of iron overload in nearly every form of hereditary hemochromatosis and non-transfused iron overloading anemia's. Analogs of hepcidin have also been seen reducing the toxicity of the iron-mediated tissue in mouse models [4]. Agonists of hepcidin known as Mini-hepcidins are based on peptides that are rationally planned, based on the hepcidin field engaging with the ferroportin. Mini-hepcidin may be helpful in iron excessive conditions used for treatment or chelation treatment. Analogs of normal hepcidin and mini-hepcidin are studied for preventing the overloading of iron in hemochromatosis and beta-thalassemia. As deficiency in hepcidin causes an overload of iron It would be expected that agents capable of mimicking hepcidin action or potentiating its endogenous production would inhibit iron.

The treatment by gene therapy of genetic conditions such as sickle cell anemia and beta-thalassemia will prevent blood transfusions and reduce iron overload in the tissues. In individuals with hereditary hemochromatosis and beta-thalassemia including the DMT-1 activation and gene expression of ferroportin in enterocytes Over-expression

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of the wild-type HFE gene in enterocytes and overexpression of the iron regulatory peptide hepcidin in the liver are other therapeutic strategies that could be studied [5]. The HFE genotype may influence the survival of myelodysplastic syndrome patients and tests need to be carried out if these patients are to be treated with effective iron chelation therapy.

CONCLUSION

In the Indian subcontinent, the common genetic disorder is Thalassemia. Hyper-transfusion has improved the expected lifespan of thalassemic patients over the decades, but the excessive number of blood transfusions ensures iron overload is inevitable complication major in thalassemia patients. Several studies have concluded that liver cirrhosis is associated with increased levels of serum ferritin. Iron is an essential component in biochemical and biological processes, however, when excess, oxidative stress can lead to tissue damage. Excess iron in the body can cause damage to organs such as liver, spleen, liver, bone marrow, pancreas, pituitary gland and nervous system.

In the last 20 years, thalassemia major management has developed to the point where the life expectancy of patients is as high as normal inhabitants. Therapies that reduce transfusion demands in TDT and remove insufficient erythropoiesis in NTDT may in this way be promising. Specific disruptions in factors like BCL11A that may potentially lead to γ-globin genes being kept suppressed may result in simpler and safer treatment of β-thalassemia, depending on transfusions or non-transfusions. The developmental stage-specific BCL11A repressor regulates the expression of hemoglobin. Use of strengthened activin receptors to enhance delay erythropoiesis by functioning as ligand traps for the participants in the transformation of superfamily growth factor is also a promising method, currently being tested in clinical studies. Therapy with these agents aims to increase hemoglobin levels and reduce the needs for the transfusion in both NTDT and TDT patients.

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