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β-thalassemia - A Review

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Review Article

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ABSTRACT

β-thalassemia is one of the hereditary blood disorder identified by anomalies in the synthesis of the beta chains of hemoglobin resulting in variable phenotypes ranging from severe anemia to clinically asymptomatic individuals. In a country like India, with the high frequency of hemoglobinopathies, causing increased burden on the society, it is necessary to control the incidence by effective steps. The knowledge about the frequency distribution of the predominant mutations in the population helped in offering prenatal diagnosis to the families. Conception rather than having an effected fetus. The hemoglobinopathies constitute a major public health problem among genetic conditions internationally, but particularly in the developing World which has the least resources for coping with the problem. It is apparent that prevention of the disease is of primary importance, not only to reduce the burden on the health services, but also to give better chance of survival to the existing patients.

INTRODUCTION

Hemoglobinopathies are a kind of genetic disorders that results in abnormal structure of one of the globin chains of hemoglobin molecules. They are inherited single gene disorders. About 10,000 children are born annually inheriting a major hemoglobin disorder [1-3]. Common hemoglobinopathies include thalassemia and sickle cell anemia. In sickle cell anemia RBC lose their normal oxygen carrying capacity. Thalassemia is an inherited autosomal recessive disorder. Thalassemia is of alpha and beta thalassemia [4-6].

In all sickle cell patients, there is only single identical base pair change in their DNA. In thalassemia, the rate of synthesis of one of the globin chain that makeup hemoglobin is reduced, this results in abnormal hemoglobin formation thus causing anemia, which is the characteristic symptom of this disease [6-9]. Thalassemia is difficult to cure;bone marrow transplantation is the only treatment for children affected with this disease. A regular blood transfusion with iron chelation therapy is the only treatment done to sustain life of the patients.

The main function of ZHX2 gene (zinc fingers and homeoboxes protein 2), it acts as a transcriptional repressor. ZHX2 is the novel candidate gene for globin regulation in erythroid cells. Over expression of ZHX2 transgene restores H19 repression on a BALB/cj background confirming that this gene is responsible for hereditary persistence of fetal haemoglobin (HPFH) [10].

The aim of this study is to diagnose these genetic diseases by cost effective methods and to reduce the burden of health care system. Blood samples were collected from thalassemia and Sickle cell society and Institute of Genetics and Hospital for Genetic Diseases. DNA was isolated by manual methods. Here specific DNA sequences of parents were amplified by PCR technique and then RFLP was done to determine genotype and the association of ZHX2 genetic variants with the severity of hemoglonopathies like β-thalassemia and sickle cell anemia. Nitric oxide levels were estimated and were found to be high in effected patients [11,12].

Sickle/β-thalassemia

In this condition, the patient has transmissible a sequence for hemoprotein S from one parent and a sequence for β-thalassemia from the opposite. The severity of the condition is decided to an oversized extent by the amount of traditional hemoprotein made by the β-thalassemia sequence (Thalassemia genes turn out traditional hemoprotein, however in variably reduced amounts). If the sequence produces no traditional hemoprotein, β^0-thalassemia, the condition is just about the image of RBC illness. Some patients have a sequence that produces atiny low quantity of traditional hemoprotein, referred to as β^+-thalassemia [13-16]. The severity of the condition is dampened once vital quantities of traditional hemoprotein square measure made by the β+-thalassemia sequence. Sickle/β-thalassemia is that the most typical reaping hook syndrome seen in individuals of Mediterranean descent (Italian, Greek, and Turkish). β-thalassemia is sort of common during this region, and therefore the RBC sequence happens in some sections of those countries. hemoprotein natural process of blood from a patient with sickle/β^0-thalassemia shows no hemoprotein A. Patients with sickle/β^+-thalassemia have Associate in Nursing quantity of hemoprotein A that depends of the extent of operate of the β^+-thalassemia sequence [17,18].

Hemoglobin e/β-thalassemia

The combination of hemoglobin E and β-thalassemia produces a condition more severe than is seen with either hemoglobin E trait or β-thalassemia trait. The disorder manifests as a moderately severe thalassemia that falls into the category of thalassemia intermedia. Hemoglobin E/β-thalassemia is most common in people of S.E [19].

α-thalassemia/Hemoglobin constant spring

This syndrome is a compound heterozygous state of the α globin gene cluster. The α globin gene cluster on one of the two chromosomes 16 has both α globin genes deleted. On the other chromosome 16, the α1 gene has the Constant Spring mutation. The compound heterozygous condition produces a severe shortage of α globin chains. The excess β chains associate into tetramers to form hemoglobin H [20-22].

Disease Name and Synonyms

Definition

β-thalassemia syndromes are a group of hereditary blood disorders characterized by reduced or absent β globin chain synthesis, resulting in reduced Hb in red blood cells (RBC), decreased RBC production and anemia. Most thalassemias are inherited as recessive traits. β -thalassemias can be classified into:

- β -thalassemia
- Thalassemia major
- Thalassemia intermedia
- Thalassemia minor
- β-thalassemia with associated Hb anomalies
- HbC/β-thalassemia
- HbE/β-thalassemia
- HbS/β-thalassemia (clinical condition more similar to sickle cell disease than to thalassemia major or intermedia)
- Hereditary persistence of fetal Hb and β-thalassemia
- Autosomal dominant forms
- β-thalassemia associated with other manifestations
- β-thalassemia-tricothiodystrophy
- X-linked thrombocytopenia with thalassemia

Epidemiology

β-thalassemia is rife in Mediterranean countries, the center East, Central Asia, India, Southern China, and therefore the Far East further as countries on the north coast of Africa and in South America. The very best carrier frequency is reportable in Cyprus (14%), Sardinia (10.3%), and geographical region. The high factor frequency of β-thalassemia in these regions is presumably associated with the selective pressure from Plasmodium falciparum protozoal infection [23-26]. Population migration and intermarriage between totally different ethnic teams has introduced Mediterranean anemia in nearly each country of the planet, together with geographic area wherever Mediterranean anemia was antecedently absent. it's been calculable that concerning 1.5% of the world population (80 to ninety million people) area unit carriers of β-thalassemia, with concerning 60,000 symptomatic people born annually, the good majority within the developing world [26-29]. The whole annual incidence of symptomatic people is calculable at one in 100,000 throughout the planet and one in 10,000 folks within the Europe. However, correct information on carrier rates in several populations area unit lacking, significantly in areas of the planet identified or expected to be heavily affected consistent with Mediterranean anemia International Federation, solely concerning 200,000 patients with thalassaemia area unit alive and registered as receiving regular treatment round the world. The foremost common combination of β-thalassemia with abnormal haemoprotein or structural haemoprotein variant with thalassemic properties is HbE/β-thalassemia that is most rife in geographical region wherever the carrier frequency is around five hundredth [30].

Signs and Symptoms

Signs and symptoms of thalassemia are due to lack of oxygen in the bloodstream. This occurs because the body doesn't make enough healthy red blood cells and hemoglobin. The severity of symptoms depends on the severity of the disease. A thalassemia silent carrier generally has no signs or symptoms of the disorder. This is because the lack of α globin protein is so small that hemoglobin works normally [31-35].

Mild Anemia

People who have α or β thalassemia trait can have mild anemia. However, many people with this type of thalassemia have no signs or symptoms. Mild anemia can make you feel tired. It's often mistaken for iron-deficiency anemia [36-40].

Mild to Moderate Anemia

People with β thalassemia intermedia have mild to moderate anemia. They also may have other health problems, such as:

- Slowed growth and delayed puberty. Anemia can slow down a child's growth and development [41].
- Bone problems. Thalassemia may make bone marrow (the spongy material inside bones that makes blood cells) expand. This causes wider bones than normal. Bones also may be brittle and break easily [42-44].

An enlarged spleen: The spleen is an organ that helps your body fight infection and removes unwanted material. When a person has a thalassemia, the spleen has to work very hard. As a result, the spleen becomes larger than normal. This makes anemia worse. If the spleen becomes too large, it must be removed [45-48].

Severe Anemia

People with Haemoglobin H disease or β thalassemia major (also called Cooley's anemia) have severe thalassemia. Signs and symptoms occur within the first 2 years of life. They may include severe anemia and other serious health problems, such as:

- Pale and listless appearance

- Poor appetite
- Dark urine
- Slowed growth and delayed puberty
- Jaundice (a yellowish colour of the skin or whites of the eyes)
- Bone problems (especially bones in the face)

Genetics

A prototypical globin gene includes 3 exons or coding blocks whose sequences code for the globin chains separated by 2 introns or intervening sequences (IVS) which are initially transcribed but not present in mature mRNA and are not translated into protein products. Intron-1 varies in length from 125 to 130 base pairs (bp) and intron-2 from 800 to 850 bp [49,50].

More than 300 mutations that can cause different forms of hemoglobinopathies have been identified all over the world. β-thalassemias are a result of mutation that can interfere with any step in the pathway of β-globin gene expression, they can effect transcription of the gene, mRNA processing or translation and post translational integrity of the β polypeptide chain [51-53].

Several studies undertaken in Indians have shown that five mutations are common among Indians and account for about 90% of the mutant alleles. These include IVS 1-5 (G-C);619 bp deletion;codon 8/9 (+G);IVS 1- 1 (G-T); and codon 41/42 (-TCTT). These are present in different parts of India in varying frequencies.

Prevalence varies from 22.8-81.4% in different regions of India. This sequence surrounds the invariant dinucleotides at the splice junctions. These sequences are involved in the IVS1-5 is the most common mutation found in Indian population and its mRNA processing. Different mutations in this sequence cause different forms of thalassemia [54-56].

The carriers of β-thalassaemia have levels of hemoglobins–A2, which can be greater than 3.5% of the total hemoglobin (3). Among the genetic factors known to affect HbF production are DNA sequence variations within the β-globin gene cluster. In particular, the (C→T) variation at position–158 upstream of the Gg globin gene, is detectable by the restriction enzyme Xmn1. The sequence variation has been shown to increase HbF levels in b-thalassaemia anaemia.

The sickle cell mutation reflects a single change in the amino acid building blocks of the oxygen-transport protein, hemoglobin. The α subunit is normal in people with sickle cell disease. The β subunit has the amino acid valine at position 6 instead of the glutamic acid that is normally present. This happens due to change of a nucleotide, adenine to thymine (GAGgGTG) of codon 6 of b-globin gene. This substitution of amino acid changes the net charge of hemoglobin, oxygen affinity and three-dimensional structure thus rendering it as unstable hemoglobin. Sickle hemoglobin gets polymerized at low oxygen tension and deforms the red blood cell from discoid shape to sickle like (crescent) form. The immune status of these patients is also reduced. Hence, they fall prey to various infective agents very easily. This alteration is the basis of all the problems that occur in people with sickle cell disease. The gene that controls the production of the β globin subunit of hemoglobin is located on one of the 46 human chromosomes (chromosome #11) [57-60].

Modifier Genes

Zinc fingers and homeoboxes2 (ZHX2) gene

The members of the zinc fingers and homeo boxes gene family are nuclear homodimeric transcriptional repressors that interact with the A subunit of nuclear factor-Y (NF-YA) and contain two C2H2-type zinc fingers and five homeobox DNA-binding domains. Zhx2 consists of 837 amino acid residues and contains 2 zinc finger motifs and 5 homeodomains. ZHX2 gene is among other candidate genes in chromosome 8q region which is identified as QTLs influencing HbF. Moreover, ZHX2 expression have shown in various tissues (Cherimoya) [59-63].

The principle capacity of the quality is it goes about as a transcriptional repressor. ZHX2 is the novel hopeful quality for globin regulation in erythroid cells. Over articulation of ZHX2 transgenic restores H19 restraint affirming that this quality is in charge of heriditory determination of α-feto protein and H19 which are translated at abnormal states in the mammalian fetal liver however are quickly stifled postnatally. ZHX2 quality agrees on the QTL chromosomes 8q yet impact outright fetal hemoglobin levels. Subsequently ZHX2 is in charge of managing γ-globin quality expression (**Figure 1**) [64].

Patients with β-thalassemia were broke down for zinc finger and homeoboxes 2 (ZHX2) G779A polymorphism, and the relationship between ZHX2 quality polymorphism and seriousness of β-thalassemia was assessed. We didn't locate a huge distinction in genotypic and allelic recurrence of ZHX2 quality in the middle of gentle and direct, mellow and serious, and moderate and extreme cases. There was no huge distinction in high and low rate of HbF in GG, GA, and AA bearing people demonstrating that ZHX2 quality variation has no part in improving the seriousness of β-thalassemia real in the South Indian populace from Andhra Pradesh.

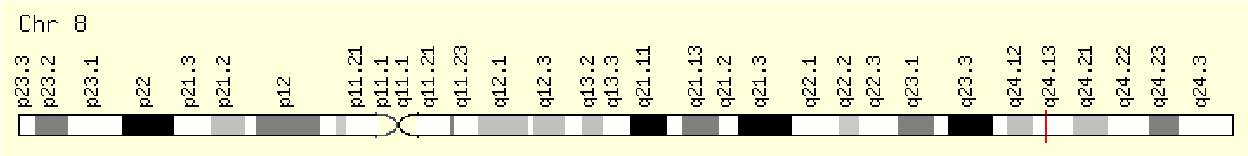

Figure 1. ZHX2 gene structure.

A thalassemia conclusion is made by utilizing blood tests, including a complete blood number (CBC), and uncommon hemoglobin studies.

The accompanying tests are utilized to screen for thalassemia:

- complete blood number
- HPLC
- Hemoglobin electrophoresis with quantitative hemoglobin A2 and hemoglobin F
- free erythrocyte-protoporphyrin (or ferritin or different investigations of serum iron levels)

A complete blood tally will distinguish low levels of hemoglobin, little red platelets, and other red platelet anomalies that are normal for a thalassemia conclusion. Since characteristic can in some cases be hard to recognize from iron lack, tests to assess iron levels are imperative. A hemoglobin electrophoresis is a test that can help recognize the sorts and amounts of hemoglobin made by a person. This test uses an electric field connected over a piece of gel-like material [65-67]. Hemoglobin's move through this gel at different rates and to particular areas, contingent upon their size, shape, and electrical charge. Isoelectric centering and superior fluid chromatography (HPLC) use comparative standards to particular hemoglobins and can be utilized rather than or as a part of different blends with hemoglobin electrophoresis to focus the sorts and amounts of hemoglobin present [68]. Hemoglobin electrophoresis results are normally inside of the typical reach for a wide range of α thalassemia. Nonetheless, hemoglobin A2 levels and once in a while hemoglobin F levels are raised when β thalassemia infection or attribute is available. Hemoglobin electrophoresis can likewise recognize basically anomalous hemoglobins that may be co-acquired with a thalassemia attribute to bring about thalassemia infection (i.e., hemoglobin E) or different sorts of hemoglobin malady (i.e., sickle hemoglobin). Now and again DNA testing is required notwithstanding the above screening tests. This can be performed to help affirm the conclusion and set up the definite hereditary sort of thalassemia [69-71].

Treatment

Patients with thalassemia minor more often than not don't require any particular treatment. Treatment for patients with thalassemia major incorporates interminable transfusion treatment, iron chelation, spleenectomy, and allogeneic hematopoietic transplantation. Patients in the heterozygous state more often than not don't oblige treatment. Illuminate patients that their condition is inherited and that doctors at times mix up the issue for iron lack some pregnant patients with the β thalassemia characteristic may create simultaneous iron inadequacy and extreme paleness. They may oblige transfusional backing if not receptive to iron repletion modalities [72-74].

Blood Transfusions

The objective of long haul hypertransfusional backing is to keep up the understanding's Hb at 9-10 μg/dL, along these lines enhancing the persistent feeling of prosperity while at the same time stifling improved erythropoiesis. This procedure treats the iron deficiency, as well as stifles endogenous erythropoiesis so that extra medullary hematopoiesis and skeletal changes are suppressed. Patients getting transfusion treatment additionally oblige iron chelation with desferrioxamine [75-77]. Blood keeping money contemplations for these patients incorporate totally writing their erythrocytes preceding the first transfusion. This technique helps future cross matching procedures.

Allogeneic hematopoietic transplantation may be healing in a few patients with thalassemia major. An Italian gathering drove via Lucarelli has the most involvement with this procedurethis bunch's examination archives a 90% long haul survival rate in patients with ideal attributes (youthful age, HLA match, no organ brokenness) [78-80].

Surgical Care

Patients with thalassemia minor seldom require spleenectomy, despite the fact that the improvement of bilirubin stones as often as possible prompts cholecystectomy [81].

Medicine

Restorative treatment for β-thalassemia essentially includes iron chelation. Deferoxamine is the intravenously managed chelation operators presently affirmed for utilization in the United States. Deferiprone is an oral chelation specialists, as of late sanction for utilization in Europe. While the consequences of studies on this oral operators are empowering, complexities of hepatic fibrosis may create Deferiprone as of now is not sanction for utilization in the United States [82-86].

Extra medicines being worked on are exploratory conventions to control globin quality expression utilizing quality treatment or utilizing medications that enact gamma-globin qualities. Since fetal globin quality expression is connected with a milder phenotype, ways to deal with improve intracellular Hb F levels (by enacting gamma-globin quality expression) are under scrutiny. The 2 most broadly examined medications here are butyrates and hydroxyurea [87-89].

In a little study, assessed the clinical and hematologic reaction to hydroxyurea in 79 β-thalassemia patients in western India with variable clinical seriousness and related the discoveries with hereditary elements. One gathering comprised of 38 β-thalassemia intermedia patients, and a second gathering comprised of 41 β-thalassemia significant patients. Both gatherings were directed hydroxyl urea treatment and caught up for 20-24 months [90-94]. Discoveries comprised of the accompanying

• Fifty-eight percent of the as often as possible transfused patients in the β-thalassemia intermedia gathering got to be transfusion autonomous. Sixteen percent exhibited a 50% diminishment in post-treatment transfusions versus 32% in the β-thalassemia real gathering, both relating with a more prominent mean fold increment in HbF and gamma mRNA expression levels [95].

• Forty-one percent of the β-thalassemia intermedia amass additionally had related α-thalassemia, and 72.7% were XmnI (+/+).

• Of β-thalassemia intermedia patients who had a clinical and hesmatologic reaction to hydroxyurea treatment, 41% had a connection to haplotype (- + - + - - +) rather than haplotype (+ - - - - - - - +), which was more basic in patients without such a reaction. Be that as it may, reaction was not connected with the β-thalassemia transformations [96].

• Both β -thalassemia gatherings demonstrated a huge diminishing in serum ferritin. Overall, the examiners found that clinical reaction to hydroxyurea in the β-thalassemia intermedia gathering was better in patients with α-thalassemia, XmnI (+/+), and a higher mean fold increment in gamma mRNA expression. In those with β-thalassemia significant, 33% demonstrated an incomplete reaction.

• Gene-substitution treatment or quality treatment is being sought after by a few exploration bunches. Impediments in quality treatment incorporate failure to express elevated amounts of the β-globin quality in erythroid cells and powerlessness to transduce hematopoietic pluripotent foundational microorganisms at high effectiveness. In a late report, one grown-up patient with serious transfusion-subordinate β-thalassemia got to be transfusion autonomous for 21 months, 33 months after lentiviral β-globin quality exchange, with fringe blood hemoglobin.

Deferoxamine (Desferal)

Adult 20-40 mg/kg/d SC infused over 8-12 h;may be administered IV/IM if necessary.

Paediatric: Administer as in adults Co administration of vitamin C improves iron chelation (vitamin C is contraindicated in patients with heart failure because it may exacerbate cardiac dysfunction Documented hypersensitivity;patients who do not have acute iron poisoning;severe renal disease and anuria (consider dose reduction after the loading dose) [97].

Medications and Fetal Haemoglobin

Another form of gene therapy for thalassemia major could involve using drugs or other methods to reactivate the patient's genes that produce fetal hemoglobin, which is the form of hemoglobin found in fetuses and new-borns [98].

Scientists that spurring production of fetal hemoglobin will compensate for the patient's deficiency of adult hemoglobin.

Thalassemia Prevention and Management

α and β-thalassemia are often inherited in an autosomal recessive fashion although this is not always the case. A prerequisite for a successful prevention and control programmer requires:

- Public awareness
- Population screening for carriers
- Genetic counseling
- Prenatal diagnosis

Public awareness

Educating people about thalassemia and hemoglobinopathies by conducting meetings and seminars, write-up's in magazines and newspapers, publishing newsletters, radio and television programs, video films, workshops, exhibition and distribution of literature on thalassemia [99].

Population Screening for Carriers

Having taken efforts to educate the people about thalassemia and hemoglobinopathies, one also has to screen the population by accurate and reliable test at an affordable cost. Screening for Hb variant protein has been carried by electrophoresis, micro chromatography, isoelectrofocussing or HPLC (high performance liquid chromatography).

Other Complications

Cardiac disease

In the past few years, particular attention has been directed to the early diagnosis and treatment of cardiac disease because of its critical role in determining the prognosis of individuals with β-thalassemia. Regular blood transfusions are a standard treatment for thalassemia.

Infection

Among people who have thalassemia, infections are a key cause of illness and the second most common cause of death.

Endocrinologic diseases

Endocrinologic complications are well documented in patients with hemoglobinopathies requiring frequent and recurrent blood transfusion. The most common findings are delayed puberty and growth failure. Less commonly seen are bone loss, hypothyroidism, and hyperglycemia [100].

Pulmonary hypertension

A high prevalence of pulmonary hypertension is associated with sickle cell hemoglobinopathy (SCH) with consequent high mortality.

Splenic sequestration

For unknown reasons, large amounts of blood may suddenly pool in the liver and spleen. Signs of shock or circulatory collapse develop rapidly, and death may occur. If the patient is supported by hydration and by blood transfusion, the sequestered blood may be remobilized.

CONCLUSION

In a country like India, with the high frequency of hemoglobinopathies, causing increased burden on the society, it is necessary to control the incidence by effective steps. Implementation of carrier screening program offering genetic counseling and prenatal diagnosis followed by selective termination of affected cases would help in preventing the disease. Similar approach in other countries like Greece, Cyprus and Sardina resulted in a marked reduction in the birth rate of affected children. The present study was taken up to detect the prevalence of the disease in Andhra Pradesh and also to detect the point mutations and frequency analysis.

The knowledge about the frequency distribution of the predominant mutations in the population helped in offering prenatal diagnosis to the families having foetus at risk. Some of the families who needed immediate fetal diagnosis were advised prenatal diagnosis. Prospective counseling was given to unmarried people (especially carriers) to instill awareness in them and encouraging caution during partner selection.

In Andhra Pradesh, the conservative families marry their children within the same caste and community also perform consanguineous marriages, therefore certain communities/castes tribes show high incidence of these disorders. Therefore, counseling for screening before marriage needs to be encouraged in order to avoid the mental and physical trauma along with the financial burden of an affected child. Though prenatal diagnosis is available for the fetus at risk, it is advisable to prevent the conception rather than having an effected featus.

The hemoglobinopathies constitute a major public health problem among genetic conditions internationally, but particularly in the developing World which has the least resources for coping with the problem. It is apparent that prevention of the disease is of primary importance, not only to reduce the burden on the health services, but also to give better chance of survival to the existing patients. Preventive programs consisting of public education, population screening, genetic counseling and prenatal diagnosis have been very effective in reducing the birth rate of β-thalassemia major.

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