

A REVIEW ON: B-THALASSEMIA

Ramdas Malakar*, Manpreet Kour, S. N. Malviya and C. B. S. Dangi

Department of Biotechnology, RKDF University Bhopal (M.P.) India.

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*Corresponding Author

Ramdas Malakar

Department of
Biotechnology, RKDF
University Bhopal (M.P.)
India.

ABSTRACT

The thalassemias represent the most common single gene disorder worldwide. The total annual incidence of symptomatic individuals with β -thalassemia is estimated at 1 in 100,000 throughout the world. 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, so, it is important to take into consideration this disorder

as it may prove deadly one. The intensity of this disorder can be lowered prenatal diagnosing and taking preventive measures. The present work summarizes β -thalassemia, epidemiology, causes and complication of this disorder.

KEYWORDS: β -thalassemia, β -globin, epidemiology, etiology and complication.

INTRODUCTION

The term "thalassemia" is derived from the Greek words "Thalassa"(sea) and "Haema" (blood) and refers to disorder associated with defective synthesis of α or β -globin subunits of haemoglobin (Hb)A($\alpha_2\beta_2$), inherited as pathologic alleles of one or more of the globin genes located on chromosomes 11 (β) and 16 (α). More than 200 deletions or point mutations that impair transcription, processing or translation of α or β -globin m-RNA have been identified. The clinical manifestations are diverse, ranging from absence of symptoms to profound fatal anemias in utero or if untreated, in early childhood (Sandhya *et al.*, 2013). β -thalassemia syndromes are a group of hereditary blood disorders characterized by reduced or absent beta globin chain synthesis, resulting in reduced Hb in red blood cells (RBC), decreased RBC

production and anemia. Most thalassemias are inherited as recessive traits (Galanello *et al.*, 2010).

In the past 20 years, the two important forms of this disorder, α - and β -thalassemia, resulting from the defective synthesis of the α - and β -globin chains of hemoglobin, respectively, have become recognized as the most common monogenic diseases in humans (Weatherall *et al.*, 1996). This article focuses on the β -thalassemias, the severe forms of which are by far the most important of all the thalassemias. The molecular and clinical aspects of the severe α -thalassemia syndromes have been reviewed elsewhere (Nancy. *et al.*, 1999 & Chui *et al.*, 1998).

CLINICAL FORM OF β -THALASSEMIA

The β -thalassemias include four clinical syndromes of increasing severity: two conditions are generally asymptomatic, the silent carrier state and β -thalassemia trait, Usually results from the inheritance of one mutant β -globin gene, and two require medical management, thalassemia intermedia and thalassemia major. The more other forms most often result from homozygosity or compound heterozygosity for a mutant β -globin allele and occasionally from heterozygosity for dominant mutations (Thein *et al.*, 1990). Homozygous or compound heterozygous β -thalassemia usually presents no diagnostic problems. In other two conditions early onset of anemia, characteristic blood changes and elevated fetal hemoglobin concentrations are found in no other condition. The diagnosis can be confirmed by the demonstration of the β -thalassemia trait in both parents. This condition is characterized by mild anemia, reduced mean cell volumes and mean cell hemoglobin concentrations and elevated concentrations of the normal minor adult component of hemoglobin (usually exceeding 3.5 percent), hemoglobin A₂ ($\alpha_2\delta_2$). Thalassemia major and thalassemia intermedia have no specific molecular correlate but encompass a wide spectrum of clinical and laboratory abnormalities (Camaschella *et al.*, 1995 & Nancy *et al.*, 1999).

The phenotypes of homozygous or genetic heterozygous compound β -thalassemias include thalassemia major and thalassemia intermedia. Individuals with thalassemia major usually come for medical attention within the first two years of life and require regular RBC transfusions to survive. Thalassemia intermedia include patients who present later and do not require regular transfusion. Except in the rare dominant forms, heterozygous β -thalassemia results in the clinically silent carrier state. HbE/ β -thalassemia and HbC/ β -thalassemia

exhibit a great range in terms of diversity of phenotypes and spectrum of severity (Galanello *et al.*, 2010).

EPIDEMIOLOGY

Worldwide, patients with haemoglobin E-beta-thalassaemia (Hb E/ β -thalassaemia) represent approximately 50 per cent of those affected with severe β -thalassaemia¹⁻⁷. The highest frequencies are observed in India, Bangladesh and throughout Southeast Asia, particularly in Thailand, Laos and Cambodia, where it is common for individuals to inherit alleles for both haemoglobin E (Hb E) and β -thalassaemia. Throughout these regions, Hb E/ β -thalassaemia has become an increasingly severe public health problem. In Thailand, about 3,000 affected children are born annually and estimates of about 100,000 living patients have been provided (Nancy *et al.*, 2011). The true prevalence has estimated 5-7% of the population worldwide carries clinically significant hemoglobin mutation. β -thalassemia is most commonly found in the population of southern Europe, southeast Asia, Africa and India, α -thalassemia is widespread in Africa and Mediterranean population, the Middle East and Asia (Navaneet *et al.*, 2013).

ETIOLOGY

Thalassemia is directly linked to genes and how the genes that affect haemoglobin production are inherited. People with moderate to severe forms received variant genes from both parents. People who are carriers of the disease received variant genes from one parent and normal gene from the other parent (Galanello *et al.*, 2010). This disorder is caused from a mutation or deletion of the globin production gene which leads to decreased production (Alan *et al.*, 2004). As a result, the globin protein chains make an abnormal haemoglobin amount which decreases the synthesis of haemoglobin. The quantity of the disruptions in the chain synthesis determines the severity of the Thalassemia (Eliezer *et al.*, 2011 & Sandhya *et al.*, 2013). More than 200 mutations have been so far been reported; the large majorities are point mutations in functionally important regions of the beta globin gene (Giardine *et al.*, 2007). Deletions of the β -globin gene are uncommon. The β -globin gene mutations cause a reduced or absent production of β -globin chains. A list of common mutations according to the severity and ethnic distribution is reported (Galanello *et al.*, 2010). 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. 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 (Ghodekar *et al.*, 2010).

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) (Ghodekar *et al.*, 2010).

MOLECULAR PATHOLOGY

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 (Ghodekar *et al.*, 2010).

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 β -like globin genes arranged in a link cluster over 60 kilobases (kb). A critical control region of the β -globin gene (promoter) is known to be defective; it inhibits messenger RNA (mRNA) processing, resulting in only a small amount of Hb A₂ ($\alpha_2\delta_2$) 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 $\alpha/\alpha_2/\alpha_1$ (Ghodekar *et al.*, 2010).

TYPES OF BETA THALASSEMIA

Heterozygous β^+ thalassemia or thalassemia minor: Carriers of β -thalassemia are clinically asymptomatic. The characteristic hematological features are microcytosis (reduced red blood cell volume), hypochromia (reduced red blood cell Hb content) and increased HbA₂ level (Sandhya *et al.*, 2013, Galanello *et al.*, 2010 & Grow *et al.*, 2014).

Homozygous β^0 thalassemia or thalassemia major

Individuals with thalassemia major usually present within the first two years of life with severe anemia, requiring regular red blood cell [RBC] transfusions. Findings in untreated individuals with thalassemia major are growth retardation, pallor, jaundice, poor musculature, hepatosplenomegaly, leg ulcers, development of masses from extramedullary hematopoiesis, and skeletal changes that result from expansion of the bone marrow. Peripheral blood smear shows, in addition to microcytosis and hypochromia, anisocytosis, poikilocytosis [spiculated tear drop and elongated cells] and nucleated red blood cells [i.e., erythroblasts]. Hb pattern [by cellulose acetate electrophoresis or high performance liquid chromatography [HPLC]] varies according to the type of β -thalassemia. In β -thalassemia, characterized by the lack of β -globin chain synthesis, HbA is absent, HbF is 95–98%, and HbA2 is 2–5% (Sandhya *et al.*, 2013, Galanello *et al.*, 2010 & Grow *et al.*, 2014).

Thalassaemia (delta- β) intermedia

Patients have a moderate anemia and show a markedly heterogeneous hematological picture, ranging in severity from that of the β -thalassemia carrier state to that of thalassemia major (Sandhya *et al.*, 2013, Galanello *et al.*, 2010 & Grow *et al.*, 2014).

Dominant beta-thalassemia

In contrast with the classical recessive forms of beta-thalassemia, which lead to a reduced production of normal beta globin chains, some rare mutations result in the synthesis of extremely unstable beta globin variants which precipitate in erythroid precursors causing ineffective erythropoiesis. These mutations are associated with a clinically detectable thalassemia phenotype in the heterozygote and are therefore referred to as dominant beta-thalassemias (Thein 1992). The presence of hyper-unstable Hb should be suspected in any individual with thalassemia intermedia when both parents are hematologically normal, or in families with a pattern of autosomal dominant transmission of the thalassemia intermedia phenotype. Beta globin gene sequencing establishes the diagnosis (Galanello *et al.*, 2010).

Silent β -Thalassemia

Mainly by minimal deficit of β -globin gene, silent type β -thalassemia is produced. Generally in homozygous condition, a typical β -thalassemia like condition is found or in case of compound heterozygous thalassemia intermedia like symptom is observed. It is very rare to find the alleles for silent β -thalassemia, except C→T and C→G mutation in β -globin gene

at101 position, IVS II 844 (C→G) in heterozygous carrier state 19 (Bianco *et al.*, 1917 & Panja *et al.*, 2012).

CARRIER OF β -THALASSEMIA

The frequency of β -thalassemia carrier varies between 1 to 17 percent in different region in India with mean prevalence of 3.3 percent. In multicentric ICMR study, the carrier frequency was reported to be 5.5 percent in Delhi, 4 percent in Mumbai and 7 to 8% percent in Kolkata. This calculates to about 29.7 million carriers of β -thalassemia in India. Using these carrier frequencies, it can be estimated that almost one out of every 2,700 births has thalassemia major, while almost 9,000 newborn with thalassemia major are born every year. Migration changing marriages pattern among ethnic group, and differences in the relative growth of population can be expected to change the distribution and prevalence of thalassemia.

β -THALASSEMIA IN INDIA

β -thalassemia is the commonest single-gene disorder in the Indian population (Verma 1994). Ten percent of the total world thalassemics are born in India every year (Bashyam *et al.*, 2004). Certain communities in India, like Sindhis, Gujratis, Punjabis and Bengalis, are more commonly affected with β -thalassemia, the incidence varying from 1 to 17% (Gupta *et al.*, 2003). It has been estimated that the prevalence of pathological hemoglobinopathies in India is 1.2/1,000 live births (Christianson *et al.*, 2006) and with approximately 27 million births per year (Grow *et al.*, 2014). Around 7% of the world populations are carriers of globin gene mutations in the α or β -globin gene clusters (Forget *et al.*, 2001). In view of above, Indian Red Cross Society, Gujarat State Branch carried out population screening for β -Thalassemia, during the period from 2004 -2011. It was observed from the carrier screening that 1000 infants are born each year with homozygous β -Thalassemia disorder in Gujarat (Sheth *et al.*, 2008) Hence there is need to develop cost effective diagnosis technique for prenatal diagnosis (Shrivastava *et al.*, 2012).

PATHOPHYSIOLOGY OF ANEMIA IN β -THALASSEMIA

Thalassemia is a disorder of haemoglobin synthesis which is characterized by the absence or reduced synthesis of globin chains, $\alpha, \beta, \delta, \gamma, \zeta$ and ϵ of human haemoglobin (Hb). The two main types of thalassemia are α and β -thalassemia. Phenotypically these two forms of β -thalassemia: β^0 -no β -globin chain synthesis, and β^+ -with some β -globin chain synthesis. Clinically, thalassemia presents as β -thalassemia trait (minor) (β^+ or β^0), intermedia (β^+/β^+ ; β^+/β^0) or major (β^0/β^0). β -thalassemia trait (minor) is usually asymptomatic and is associated

with the inheritance of a single gene defect. β -thalassemia major results in severe transfusion dependent anemia and is caused by the inheritance of two β -globin gene mutations either in a compound heterozygous or homozygous state. β -thalassemia intermedia is of moderate severity and the majority of affected individuals do not require regular blood transfusions (Elizabeth *et al.*, 2010). Thalassaemia major requires life-long blood transfusion and bears risks of transfusion haemosiderosis, but it is amenable to prenatal diagnosis. The affected child appears to be normal at birth, when foetal haemoglobin ($\alpha^2 \gamma^2$) is still the major component in the red blood cells. At around 6 months of age, the child becomes progressively anaemic because of the failure to produce adult haemoglobin ($\alpha^2 \beta^2$). To sustain life and normal growth, the child must be given a blood transfusion at regular intervals (Lee *et al.*, 1998). Hemoglobin E-beta thalassemia is common hemolytic anemia in Southeast Asia (Lukens *et al.*, 1993). HbE (β -26 glutamine \rightarrow lysine) is commonest hemoglobin variant in India with prevalence of 7-50% in Northeastern region and 1-2% in West Bengal (Piplani 2000). HbE may not be of clinical significant, but interaction of HbE and thalassemia produces variable phenotype (Beutler *et al.*, 2001). The thalassemia phenotype of HbE is due to activation of cryptic donor splice site by the mutation (Panigrahi *et al.*, 2005).

β -THALASSEMIA ASSOCIATED WITH OTHER Hb ANOMALIES

The interaction of HbE and β -thalassemia results in thalassemia phenotypes ranging from a condition indistinguishable from thalassemia major to a mild form of thalassemia intermedia. Depending on the severity of symptoms three categories may be identified:

Mild HbE/beta-thalassemia

It is observed in about 15% of all cases in Southeast Asia. This group of patients maintains Hb levels between 9 and 12 g/dl and usually do not develop clinically significant problems. No treatment is required (Galanello *et al.*, 2010).

Moderately severe HbE/ β -thalassemia

The majority of HbE/ β -thalassemia cases fall into this category. The Hb levels remain at 6-7 g/dl and the clinical symptoms are similar to thalassemia intermedia. Transfusions are not required unless infections precipitate further anemia. Iron overload may occur (Galanello *et al.*, 2010).

Severe HbE/ β -thalassemia

The Hb level can be as low as 4-5 g/dl. Patients in this group manifest symptoms similar to thalassemia major and are treated as thalassemia major patients (Galanello *et al.*, 2010 & Panja *et al.*, 2012).

HbC/ β -thalassemia

The Patients of HbC/ β -thalassemia generally suffers from anaemia and splenomegaly. Hbc crystal bodies can be identified in blood film, microcytosis and hypochromia is found (Panja *et al.*, 2012). HbC/ β -thalassemia may live free of symptoms and be diagnosed during routine tests. When present, clinical manifestations are anemia and enlargement of the spleen. Blood transfusions are seldom required. Microcytosis and hypochromia are found in every case. The blood film shows distinctive Hb C crystals with straight parallel edges, target cells and irregularly contracted cells with features of thalassemia such as microcytosis (Panja *et al.*, 2012 & Galanello *et al.*, 2010).

β -THALASSEMIA ASSOCIATED WITH OTHER FEATURES: In rare instances the β -thalassemia defect does not lie in the beta globin gene cluster. In cases in which the β -thalassemia trait is associated with other features, the molecular lesion has been found either in the gene encoding the transcription factor TFIIH (β -thalassemia trait associated with trichothiodystrophy) or in the X-linked transcription factor GATA-1 (X-linked thrombocytopenia with thalassemia) (Viprakasit *et al.*, 2001, Freson *et al.*, 2002 & Galanello *et al.*, 2010).

Hereditary transmission

The β -thalassemias are inherited in an autosomal recessive manner. The parents of an affected child are obligate heterozygotes and carry a single copy of a disease-causing β -globin gene mutation. At conception, each child of heterozygotes parents has 25% chance of being affected, 50% chance of being an asymptomatic carrier and 25% chance of being unaffected and not carrier. The parents of the pro-band have a 1 in 4 (25%) risk of having further affected children in each pregnancy (Sandhya *et al.*, 2013). Dominant forms of β -thalassemia, associated with mutations that result in the production of highly unstable β -globulin variants and leading to a clinically manifesting phenotype of β -thalassemia in heterozygotes, have been discussed above in the clinical description section (Thein 1992 & Galanello *et al.*, 2010).

Clinical features of thalassemic syndromes

- Fatigue
- Weakness
- Shortness of breath
- Pale appearance
- Irritability
- Facial bone deformities
- Yellow discoloration of the skin (jaundice)
- Slow growth
- Protruding abdomen
- Dark urine

Complications of β -thalassemia

Common complications include heart disease (heart failure and arrhythmias), chronic liver disease, 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 complication is decreasing due to blood transfusion advent of new oral iron chelators and imaging method. In addition, therapy for several other complications is available (Borgan *et al.*, 2010 & Navaneet Krishnan *et al.*, 2013).

β -thalassemia major patients may need to have repeated blood transfusions throughout their life for survival, which leads to so many complications. These relate to inadequate transfusions, transfusion-related infections, allow sensitization, iron-overload related cardiac, endocrine and liver disturbances and toxicities of iron chelators (Agarwal 2004). Many of these problems are strongly age dependent. Heart disease is the most important complication and the main determinant of survival (Dimitrios *et al.*, 2001). It is responsible for more than half of the deaths. It may take the form of cardiomyopathy, pulmonary hypertension, heart failure, arrhythmias, pericarditis and myocarditis (sandhya *et al.*, 2013 & Samira *et al.*, 2013).

PREVENTION**Creating awareness**

Creating awareness about thalassemia to the general population, it is necessary for the government and medical communities by holding seminars, workshops and writing articles in

the daily newspapers, broadcasting in television and radio is of prime importance for the awareness of local population.

Genetic counseling

At risk individuals must be provided with information and risk couples (i.e. both carriers) regarding the mode of inheritance, the genetic risk of having affected children and the natural history of the disease including the available treatment and therapies under investigation (Rahman *et al.*, 2003).

Prenatal diagnosis

Acceptance of prenatal diagnosis and termination of affected foetuses are dependent on the early identification of couples at risk. Prenatal diagnosis for pregnancies at increased risk is possible by analysis of DNA extracted from foetal cells obtained by amniocentesis, usually performed at approximately 15-18 weeks' gestation (sandhya *et al.*, 2013).

or chorionic villi sampling at 11 weeks' gestation. Both disease-causing alleles must be identified before prenatal testing can be performed. New technology using foetal DNA obtained from maternal plasma or maternal peripheral blood has also been developed but is not routinely available (Colah *et al.*, 2011).

CONCLUSIONS

Thalassaemia major imposes highly clinical, psychological burden on the patients and economical burden their family and hence this article briefly describes the epidemiology, types, clinical features, diagnosis and management of the β -thalassemia. From the information known so far said it can be well that the Thalassemia is a dangerous disorder which is spreading worldwide important point 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. The marked increase in survival, to the fifth decade of life, of patients with well-managed β -thalassemia in developed countries represents one of the most dramatic alterations in morbidity and mortality associated with a genetic disease but in our county 75 years after the fascinating initial description of "peculiar bone changes" and other signs and symptoms of

the disorder, the β -thalassemias have emerged as a huge public health problem worldwide. They remain a therapeutic challenge for the next millennium.

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