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**Mawlood B. Kowash, BDS, MSc, PhD, FRCDC, FDSRCPS**

Associate professor in pediatric dentistry, Mohammed Bin Rashid University of Medicine and Health Sciences, United Arab Emirates

## Review Article

# Medical and Dental Implications of Patients with Beta Thalassaemia Major. Part I: General and Medical Characteristics: A Review

**Shaikha Al Raeesi, Mawlood Kowash\*, and Manal Al Halabi**

*Department of Paediatric Dentistry, Mohammed Bin Rashid University of Medical and Health Sciences, UAE*

## Abstract

Thalassaemia is one of the most common inherited haemoglobinopathies characterized by either a partial or a complete suppression in the production of normal haemoglobin as a result of defective synthesis of one or more of the globins chains. Thalassaemia is the most widely distributed genetic disorder. Approximately 5 % of the world's population was found to have a globin variant, with only 1.7 % having an alpha or beta thalassaemia trait. The Mediterranean region, the Middle East, the Indian subcontinent and Far East Asia show the highest rates of prevalence of beta thalassaemia. Beta thalassaemia is considered to be a major public health issue, as well as a life threatening condition characterized by severe anaemia, hepatosplenomegaly, growth retardation, endocrine dysfunction, cardiac failure and skeletal changes.

Management strategies using blood transfusion and chelation therapy will improve the control of anaemia, suppression of erythropoiesis, and inhibition of gastrointestinal iron absorption of beta thalassaemia major patients. Bone marrow transplant is considered an excellent curative therapy in thalassaemic patients during childhood, which will provide prolonging life expectancy.

This paper reviews the literatures and discusses briefly the definition, history, epidemiology, classification, aetiopathogenesis, general manifestation and general management of beta thalassaemia major.

## \*Corresponding author

Kowash M, Associate Professor in Paediatric Dentistry, Hamdan Bin Mohammed College of Dental Medicine, Mohammed Bin Rashid University of Medical and Health Sciences, Dubai, UAE, Tel: 00971 505939004;

Email: mkowash@gmail.com

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## INTRODUCTION

Haemoglobinopathies are the most common autosomal recessive inherited diseases in humans with an estimated 240 million carriers worldwide, therefore thalassemia is one of the most common haemoglobinopathies as well as the most widely distributed genetic disorder [1].

Thalassemia refers to a group of inherited haematologic disorders caused by defects in the synthesis of one or more polypeptide chains of haemoglobin. Haemoglobin consists of an iron-containing haeme ring and four globin chains: two of each alphas and non-alphas. Fetal haemoglobin (HbF) has two alpha and two gamma chains (alpha<sub>2</sub> gamma<sub>2</sub>), while Adult haemoglobin A (HbA) has two alpha and two beta chains (alpha<sub>2</sub> beta<sub>2</sub>). The transition from gamma globin synthesis (HbF) to beta globin synthesis (HbA) begins before birth; by approximately six months of age, healthy infants will have mostly transitioned to HbA [2].

Approximately 5 % of the world's population was found to have a globin variant, with only 1.7 % having an alpha or beta thalassemia trait [3]. Thalassemia affects both men and women equally, and occurs in approximately 4.4 of every 10,000 live births [2].

Many studies show the highest rates of prevalence of beta thalassemia are in the Mediterranean region, the Middle East, the Indian subcontinent and Far East Asia, with prevalence rate of around 15–20% in Greece, Turkey, Cyprus, and southern Italy [4]. However, because of population migration, thalassemia has spread to Continental Europe, the North and South Americas, as well as Australia [5].

Beta thalassemia is considered to be a major public health issue, as well as being a life threatening condition characterized by severe anaemia, hepatosplenomegaly, growth retardation, endocrine dysfunction, cardiac failure and skeletal changes [6]. The hypertrophy and expansion of erythroid marrow is reflected at the skeletal level, and especially in the facial bone.

Thalassemia major patients may suffer from anaemia as a complication in early childhood. Multiple blood transfusions can prolong lives to the age of 15-25 years old and improve growth. However, death may occur due to cardiac complications of iron overload as a result of these transfusions [7].

This paper review briefly: the definition, epidemiology, pathogenesis and the general and medical characteristic of thalassemia.

## LITERATURE REVIEW

### Definition

The thalassaemia syndromes are a heterogeneous group of inherited conditions characterized by either partial or complete suppression in the production of normal haemoglobin as a result of defective synthesis of one or more of the globins chains [8].

In addition, the disease shows an anomaly of red blood cells (RBCs) which manifests as an autosomal recessive hereditary trait. This affects the alleles of one or more of the globin genes, located on either chromosome 11 or chromosome 16. This

trait was accidentally observed in the heterozygous group (thalassaemia minor), the mild form of the disease. However in the severe form of the disease, homozygous group (thalassaemia major) [8], it is observed that the red blood cells have a shortened life span, and contain fetal haemoglobin [9]. The term "thalassaemia intermedia" is used to describe the disorder with manifestations of the trait which are milder than the major form but more severe than the minor form [10].

Thalassaemia is considered a haemoglobinopathy. Haemoglobinopathies are a group of disorders, which result from an inherited abnormality of globin production, and are classified in two subdivisions; thalassemia, and sickle cell anaemia. Thalassaemia consists of an inherited defect in the rate of synthesis of one or more of the globin chains, which results in imbalanced globin chains production, ineffective erythropoiesis, haemolysis and variable degrees of anaemia. Sickle cell anaemia results from an inherited structural alteration in one of the globin chains [10].

Thalassaemia has different types which will be discussed in the classifications; the most common type in the Middle East region is the beta thalassaemia [11].

### Definition of beta thalassemia syndrome

Beta thalassaemia disorders are a group of hereditary blood disorders characterized by reduced or absent synthesis in beta globin chains. This results in reduced haemoglobin (Hb) in the red blood cells (RBCs), decreased RBC production, and anaemia. Most thalassaemia is inherited as a recessive trait [12].

### History

Thomas Cooley and Lee first recognized the clinically severe form of anaemia that was associated with splenomegaly and bone change in 1925 [10].

Wipple and Bradford first used the term Thalassaemia in 1932, derived from the Greek words "thalassa" meaning sea, and "haemia" meaning blood. In 1940, the genetic characteristics of the disease were fully understood [10].

### Epidemiology

Most studies demonstrate that the rate of prevalence of beta thalassaemia major are disseminated, with high incidence (2.5%-25%), in the Mediterranean basin, the Middle East, along with the tropical and subtropical regions of Africa, the Asian subcontinent, and Southeast Asia. The milder form of the disease is the most commonly observed [13], with the highest prevalence rate of around 15–20% in Greece, Turkey, Cyprus, and southern Italy [14]. However, due to extensive migration of the high gene occurrence population, thalassaemia has spread to Continental Europe, North and South America and Australia [5]. It has been estimated that carriers of beta thalassaemia comprise about 1.5% of the international population (between 80 to 90 million), with about 60,000 symptomatic individuals born each year. The great majority of these symptomatic individuals are in the developing world; the total incidence of symptomatic individuals annually is estimated at 1 in 100,000, and 1 in 10,000 in the European Union. However, accurate data on carrier rates among many populations is lacking, especially in regions of the world it is anticipated this would be the case [15].

According to the Thalassemia International Federation 2014, approximately 7% of the global population are carriers for haemoglobin disorders. Each year, between 300,000 and 500,000 children are born with severe haemoglobin disorders. Only around 200,000 patients with thalassaemia major are presently alive and registered as receiving regular treatment around the world [16].

## CLASSIFICATION OF THALASSEMIA SYNDROME

### Genetic classification

This disorder is generally inherited as alleles of one or more of the globin genes – located on either chromosome 11 (for beta, gamma and delta) or on chromosome 16 (for alpha chain) – are either reduced or completely absent. These deformities can result in two types of thalassaemia [17].

### Alpha thalassaemia

Alpha thalassaemia is the result of deficient or absent alpha globin chain production, leading to an increase in the amount of beta globin chains. Alpha globin chain production is controlled by two genes on each chromosome 16.

### Alpha thalassaemia has four forms

- I. **Silent carrier alpha thalassaemia:** A condition characterized by a single gene deletion, resulting in the asymptomatic alpha thalassaemia condition, with normal hematologic findings.
- II. **Alpha thalassaemia trait (mild):** A condition characterized by a two-gene deletion, with microcytosis and, usually, no anaemia.
- III. **Haemoglobin H disease (alpha thalassaemia intermedia):** The three alpha genes are deleted, resulting in significant production of haemoglobin H (HbH), containing four beta chains (beta4), and causes significant manifestations such as anaemia, haemolysis, and splenomegaly.

**Alpha thalassaemia major with HB Bart's:** The deletion of four alpha genes results in the significant production of haemoglobin Bart's (Hb Bart's) contains four gamma chains (gamma4). This produces a serious condition resulting in fatal hydropsfetalis [2].

### Beta thalassaemia

Beta thalassaemia is caused by a deficiency or absence of beta globin chain production, resulting in an excess of alpha chains. Beta globin synthesis is controlled by one gene on each chromosome 11. The severity of beta thalassaemia is dependent, to some extent, on the kind of beta thalassaemic genes that an affected individual has inherited [2].

Beta thalassaemia is the most common type of thalassaemia that occurs in the Middle East region. For this reason, we will limit our review and study to this type of thalassaemia.

- I. **Beta thalassaemia minor (trait):** Is a symptomatic condition resulting from a single gene defect; manifests as microcytosis of RBCs and mild anaemia. This condition can be detected by a routine laboratory blood evaluation.

- II. **Beta thalassaemia major (Cooley's anaemia):** The synthesis through both genes is severely reduced or absent, and results in severe anaemia, a potentially life-threatening condition. The symptoms begin to develop by six months of age due to the presence of HbF at birth.
- III. **Beta thalassaemia intermedia:** The two genes are defective, resulting in a mild to moderate decrease in the synthesis of beta globin. This condition does not require any blood transfusion.

### Clinical classifications of beta thalassaemia

**Beta thalassaemia syndromes are classified into three clinical groups:**

- I- **Severe thalassaemia (major):** Clinical manifestations of thalassaemia major occur between six and 24 months of life. Affected infants fail to thrive and become progressively pale due to a low level in haemoglobin that generally reach 6 g/dl or lower [17]. The entirety of clinical features will be discussed in detail in the clinical features section.
- II- **Thalassaemia intermedia:** Thalassaemia intermedia present later in life than thalassaemia major, and presents with milder anaemia with haemoglobin levels of 7 g/dl. It is associated with mild jaundice and hepatosplenomegaly. Iron overload is constantly exhibited by increased plasma ferritin levels. Normally patients with thalassaemia intermedia do not require blood transfusions, except when they develop infections, which precipitate further anaemia. The life span of these patients is generally short [17].
- III- **Asymptomatic thalassaemia (minor):** In this type of thalassaemia, the carriers are usually clinically asymptomatic. The haemoglobin levels are either normal, or near to normal, with no jaundice or hepatosplenomegaly present.

The most common challenge encountered by asymptomatic thalassaemia patients is to receive a "thalassaemia" diagnosis without clear clarification and proper examination from the clinician. This will often result in panic in the patient [17].

### PATHOGENESIS

Beta thalassaemia is caused by any of the more than 200-point mutations in functionally important regions of the beta globin gene. There are several methods to detect the defective gene which include ARMS or dot blot analysis; the more recent analysis is direct DNA sequence analysis [8]. The beta globin gene mutations result in the reduction or absence of the production of beta globin chains. However, the deletion of the beta globin gene is rare [18].

### PATHOPHYSIOLOGY AND HAEMOGLOBINOPATHIES

The production of all types of blood cells occurs in the bone marrow, as a result of differentiation from primitive stem cells. This is a self-regulating process, with normal target distribution of cell types, and maintenance of steady-state production balanced with natural senescence and removal from the system [19].

The pluripotent stem cell matures into two common precursor lines; lymphopoietic and hematopoietic. The lymphopoietic cell becomes either B-cell or T-cell. The hematopoietic common precursor cell becomes committed to megakaryocytic cells that mature to platelets, erythroid cells that mature to erythrocytes, or the myelomonocytic cell lines [19].

The hematopoietic system can respond to demands placed on it by triggers – such as infection, immune challenges, haemorrhage, or hypoxia – by altering the production and distribution of the cell types [19].

Haemoglobin comprises of haeme (the iron-containing portion of haemoglobin) and globin (amino acid chains that form a protein). Normal haemoglobin types include two types of adult haemoglobin A: HbA1 about 95 – 98% (contain two alpha chains and two beta chains), and HbA2 about 2 – 3 % (contain two alphas and two delta chains). The other type is fetal haemoglobin (Hb F) which contains two alpha and two gamma chains. Hb F is the first haemoglobin produced by the foetus during gestation, the production of which falls to a low level shortly after birth. Haemoglobinopathies occur when point mutations or deletions in the globin genes cause changes in the amino acids which make up the globin protein, resulting in an abnormal form of haemoglobin [19].

### Pathophysiology of major beta thalassaemia

All the pathophysiologic features of thalassaemia can be related to a primary imbalance of globin-chain production, thus making the thalassaemia fundamentally different from all other genetic and acquired disorders [19].

The depression amount of (beta+) or absence of (beta0) beta globin chains production results in a relative excess of unbound alpha globin chains that precipitate, and lead to premature RBC precursors death and accelerate the apoptosis process. The latter process leads to ineffective erythropoiesis, severe microcytic hypochromic anaemia, bone marrow expansion, skeletal deformities and increased Gastrointestinal iron absorption [20]. The nature of the mutation of the beta globin gene, located on chromosome 11, determines the degree of globin chain reduction [12].

### General manifestations of beta thalassaemia major

**Anaemia:** The onset of the severe form of the Cooley's anaemia is seen in the first two years of life and is characterized by severe hypochromia and microcytosis. The child becomes symptomatic when the haemoglobin level drops to 3 to 4 g per decilitre, with signs of a yellowish pallor of skin or jaundice, general weakness, fatigue, malaise, and lethargy [21].

**Massive erythropoiesis and bone disease:** Bone resorption, extramedullary haemopoiesis and bone marrow expansion occur as a result of severe infectious erythropoiesis as a consequence of anaemia. Radiographic images can show extramedullary hematopoietic masses around the ribs and at paravertebral sites, though nosymptoms are present. On the other hand, such masses in the skull may lead to convulsion, and if present in the spinal canal may lead to paraplegia.

**Growth endocrine function:** The most noticeable defect in

endocrine function is the absence, or impairment, of secondary sexual development in thalassaemic patients (hypogonadism). Diabetes mellitus often occurs in untreated adult patients. Hypoparathyroidism and associated with bone resorption can both be treated by blood transfusion [20].

Reduced to normal growth hormone secretion is reported. However, many patients with beta-thalassaemia have been shown to have low levels of somatomedin, a factor produced by the liver in response to growth hormone which stimulates cartilage growth [22].

**Iron overload:** Nearly every cell of the human body contains iron, a vital trace element which is required for the production of haemoglobin present in red blood cells (RBCs) and myoglobin, along with playing an important role in the production of other significant proteins involved in DNA production, as well as in cell division [23]. The normal total iron content of the adult human body is 4.5 g.

Beta thalassaemia major patients have an increased accumulation of iron in blood due to multiple blood transfusions, and the breakdown of alpha chains. It was approximated that one unit of transfused RBCs contains around 250 mg of iron, despite the fact that the body cannot excrete more than 1 mg of iron per day [24]. Any iron which exceeds the iron binding capacity of transferrin appears in the plasma as non-transferrin bound iron, which is highly toxic to tissues and has the ability to damage the developmental organs such as the heart, spleen, liver, and may result in skin pigmentation, poor appetite and weight loss [25]. Providing chelation therapy to thalassaemic patients helps in preventing these complications.

**Heart:** Cardiac failure, arrhythmias, myocarditis, pericarditis, and myocardial infarction are the lead complications in thalassaemia patient which may result in death, with the primary cause being iron deposition in the heart [21].

**Liver and hepatitis infection:** Liver disease is becoming a more relevant cause of death in patients with beta thalassaemia major. Liver disease in these patients can manifest as hepatomegaly, decreased albumen concentrations, Hepatitis B and C, liver cirrhosis, and hepatocellular carcinoma. These complications are largely a result of iron overload and inadequate chelating therapy [26]. Splenomegaly and hepatomegaly may lead to protrusion of the abdomen.

**Infections:** Severe thalassaemic patients are more vulnerable to viral, bacterial and fungal infections. Accordingly, it is believed that these infections are a leading cause of death. These infections range from minor infections such as upper respiratory tract infections and diarrhoea, to more severe infections such as pneumonia and septicaemia [17].

In these cases, massive splenomegaly is a cause of major distress. Hypersplenism can cause thrombocytopenia and abnormal bleeding in thalassaemic children; however, patients who undergo therapeutic splenectomy have a very high chance of developing bacteraemia and post-splenectomy sepsis that is caused by Gram-negative bacteria [27].

Fungal infections by *Pythium* organisms can lead to arterial occlusion and gangrene of the legs. Investigations have not yet



been able to pinpoint the key mechanisms of the infection in thalassaemic disorders. In addition, infections in thalassaemia do not appear to be related to defective lymphocytes, but might have a relationship to iron overload and severe anaemia [27].

**Osteoporosis:** Osteoporosis often arises in patients with thalassaemia, reflected by marrow expansion, endocrine deficiencies, iron toxicity, and the potential toxicity of chelators. Cortical thinning and subclinical fractures, as well as problematic clinical fractures may occur; the latter with minimal trauma. A hypercoagulable state, which increases the possibility for thromboembolism, has also been described in patients with thalassaemia secondary to platelet activation, red cell membrane damage and endothelial cell activation [28].

**Preventive measure:** Beta thalassaemia major leads to serious medical, social, and financial complications for patients and their families, in addition patient's care represents a considerable financial burden for the government. Several cultural factors play role in this disease, including the high frequency of consanguineous marriages, the large family size, and the high paternal and maternal ages may contribute to the high prevalence of beta thalassaemia in the region [29].

Genetic counselling and Pre-marital Screening are necessary components of comprehensive care for patients and parents affected by all forms of thalassaemia disease and trait as well as for all populations. Aiming in reducing the incidence of children with inherited diseases, providing information and support to individuals and families with a diagnosis and/or risk of occurrence of an inherited disorder.

Nowadays premarital screening test is one of the most important strategies for prevention of genetic disorders, congenital anomalies and several medical, psychological marital problems. Isa test in which couples that are going to get married are tested for genetic, infectious and blood transmitted diseases to prevent any risk of transmitting any disease to their children [30].

### General management of beta thalassaemia major

Management strategies for beta thalassaemia major patients emphasize prolonging life expectancy, as well as using blood transfusion and chelation therapy to improve the control of anaemia, suppression of erythropoiesis, and inhibition of gastrointestinal iron absorption.

**Blood transfusion therapy:** The decision to begin blood transfusion in patients with confirmed diagnoses of thalassaemia should be based on the presence of severe anaemia, which impairs the growth and development ( $Hb < 7$  g/dl for more than two weeks, excluding other causative factors including infections). In addition, in patients with  $Hb > 7$  g/dl, other factors should be measured including facial changes, poor growth, evidence of bony expansion, and splenomegaly. Patients starting at the age of six months may be in need of blood transfusions [12].

Different transfusion regimens have been followed over time, but the most widely accepted regime aims at a pre-transfusion Hb level of 9 to 10 g/dl, and a post-transfusion level of 13 to 14 g/dl. This approach prevents growth impairment, organ dysfunctions, and bone deformities. This helps in improving normal quality of life and activity [2].

The frequency of these transfusions is generally every two to four weeks. Shorter intervals may promote reduction in blood requirement, but are contrary to an acceptable quality of life.

The frequency of blood transfusion depends on numerous factors including weight of the patient, the target increase in Hb level, and haematocrit of blood unit [31].

**Chelation:** Transfusion-dependent patients develop iron overload as there is no physiologic mechanism, which may eliminate excess iron resulting from multiple transfusions; consequently, there is a need for treatment with an iron chelator starting between five and eight years of age [32].

Currently there are three iron chelators available for use as either monotherapy or combination.

- Deferoxamine–Iron chelation binds to iron with a 1:1 ratio. It is not orally absorbed and has a very short half-life, as such; the most common form of administration is through slow subcutaneous infusion via small portable pumps.
- Deferiprone– orally administered Deferiprone binds iron at a 3:1 ratio. It is particularly effective in removing iron from the heart.

Deferasirox– This oral chelator binds to iron at a 2:1 ratio. Due to its relatively long half-life, it may be administered in a once daily dose [33].

**Bone marrow transplantation:** Bone marrow transplant is considered an excellent curative therapy in thalassaemic patients during childhood. The first successful bone marrow transplant for a thalassaemia major patient was performed in 1982 (Thomas et al, 1982); currently over 1500 transplants have been performed worldwide.[34] Hematopoietic stem cell transplantation, too, generally results in an excellent outcome in low-risk persons with no presence of liver fibrosis or hepatomegaly, and patients in regular chelating therapy [20].

### CONCLUSION

Screening couples before marriage, prenatal diagnosis, and genetic counselling of the parents are of paramount importance in controlling this disorder. These practices will lead to a significant decrease in the number of diagnosed cases of beta thalassaemia major worldwide.

Adequate knowledge about the general manifestations as well as the management of beta thalassaemia major patients are important to the development of more suitable clinical, psychological, and social support; this may help in improving general and dental treatment outcomes in these patients. The challenge for the future is to ensure that people who are born with a severe form of thalassaemia will continue to thrive, despite the fact that effective prevention eventually decreases the number of severely affected patients worldwide.

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