

INTRODUCTION

B-Thalassemia major is a hereditary hemolytic disorder characterized by a defect in the synthesis of adult hemaoglobin beta chains, resulting in ineffective erythropoiesis. Conventional management of B-thalassemia major requires regular blood transfusion. This leads to excess iron accumulation, initially in the reticuloendothelial system and subsequently in all parenchymal organs, mainly heart, pituitary gland, pancreas and gonads, resulting in serious and sometimes fatal clinical complications (*Afroditi and Vassilios, 2006*).

Frequent transfusion and subcutaneous desferrioxamine chelation therapy improve the long-term prognosis. But problems related to secondary hemosiderosis are common. These include endocrine complications, liver disease and cardiac failure (*Roth, 1997*).

The most prominent endocrine complication are growth retardation and the failure of normal pubertal development. Other disorders such as hypothyroidism, hypoparathyroidism, impaired glucose tolerance and diabetes mellitus are less frequent (*Roth, 1997*).

In the pituitary gland iron toxicity mainly affects the gonadotropine-secreting cells, therefore, in thalassemic patients; hypogonadotropic hypogonadism is a frequent abnormality (*Roth, 1997*). The degree of pituitary iron

overload has been evaluated by MRI (*Agyropoulou et al., 2001*). A heavier pituitary siderosis was found in thalassemic patients with hypogonadotropic hypogonadism than was found in those without pituitary dysfunction. Hypophyseal damage, secondary to iron overload, might be evaluated by measuring on MR the pituitary gland height, because the later has been proven to be a useful marker in the study of pituitary gland dysfunction (*Agyropoulou et al., 2001*).

Magnetic Resonance Imaging (MRI) as long been considered a potential method for assessing tissue iron overload as iron accumulation in various organs a significant reduction in signal intensity stemming from a decrease in t2 relaxation time 3. Indeed, in some organs such as myocardium and pituitary, MRI offers a noninvasive and easily accessible method for assessing both the presence and the changes in the level of iron accumulation in vivo. Various MRI techniques for evaluating iron deposition in different organs have been developed in different centers worldwide (*Afroditi, 2006*).

AIM OF THE WORK

The aim of this study was to evaluate and correlate the pituitary iron overload assessed with MRI magnetic resonance imaging with pituitary hormonal dysfunction in children and young adults with B-thalassemia major.

THALASSEMIA

Thalassemia is one of the most common single gene disorders and is widely distributed in the Mediterranean region (*Barragan et al., 2006*). Thalassemia syndromes are a heterogeneous group of inherited anemias characterized by defects in the synthesis of one or more of the globin chain subunits of the hemoglobin tetramer (*Forget, 2000*).

In 1925, Thomas Cooley and Pearl Lee described homozygous β -thalassemia. They recognized similarities in the disease entity and clinical course of severe anemia, splenomegaly, severe growth retardation, and bone changes affecting four children of Greek and Italian origin. As all early cases were reported in children with Mediterranean background the disease was termed "Thalassemia" from the Greek word "Thalassos" meaning "sea" and "emia" which means "related to blood". Over the years, the disease proved to be widely occurring throughout tropical countries (*Cooley et al., 1925*).

It represents a serious health problem, with a predicted 1000 new patients born each year (*Hussein et al, 1993*).

The first case of β -thalassemia in Egypt was reported in the 1940s by Professor El Diwany, ever since there has been increasing interest to reveal the extent of occurrence of this problematic disease in Egypt (*Selim et al.,1974*).

Prevalence and Geographical Distribution:

Thalassemia is considered the most common genetic disorder worldwide, about 3% of the world population (150 million people) carry β -thalassemia genes and in Southeast Asia 5-10% of the population carries genes for α -thalassemia (*Honig, 2004*).

According to ethnic group, α -thalassemia trait is most prevalent in south East Asia, affects 2.7% of American black newborns and less common in the Mediterranean region. β -thalassemia occurs in 5% in certain areas of Italy, Greece, Sardinia, India and 8% in American blacks (*Weatherall, 2001*).

Classification of Thalassemias:

I. β -Thalassemia:

- 1- β -thalassemia minor (thalassemia trait): heterozygous β -thalassemia is associated with no clinical abnormalities and may be mistaken for iron deficiency anemia.
- 2- β -thalassemia major: heterozygous β -thalassemia in which there is defective formation of β chain.

There are 2 types:

- a- β^0 thalassemia: complete absence of β chain.
- b- β^+ thalassemia: β chain synthesis is reduced.

3- β -thalassemia intermedia: about 10% of heterozygous-thalassemia have a syndrome of intermediate hematological severity. Those patients usually have onset of anemia after 2 years of age and they do not require regular blood transfusion.

4- IV. β -thalassemia anemia: A very mild form of β -thalassemia, which is discovered accidentally during routine investigations.

5- Other β -thalassemia syndromes: Hb-s- β -thalassemia, Hb-C- β -thalassemia and Hb-D- β -thalassemia (*Sturt and David, 1998*).

II. α -Thalassemia:

In this group of thalassemia syndromes there is decrease in α –chain synthesis due to decreased number of α globin structure genes (*Honig 2000*).

III. Hereditary persistence of fetal HB (HPFH):

No β or δ -chain synthesis. It is a group of rare conditions characterized by continued synthesis of high levels of HbF in adult life (*Bunn and Forget, 1986*).

Age of Presentation:

Patients with severe β -thalassemia are usually diagnosed between 6 months and 2 years of age when the physiological anemia of the newborn fails to improve.

Occasionally, the disease is not recognized until the age of 3 to 5 years because the infant is able to partially compensate for the marrow inability to produce hemoglobin A by prolonged production of HbF. On presentation affected infants usually have pallor, poor growth and development and abdominal enlargement (*Modell, 1984*).

Sex:

Both sexes are equally affected.

The Molecular Aspects of Thalassemia:

Thalassemias are uniquely well characterized at the molecular level because much is known about the structure of the globin genes and behavior in the developing cells (*Chao and Wang, 1996*).

The genes encoding for the α and β chains occur in clusters, the α globin cluster is found on the tip of chromosome 16 while the β globin gene spans 7kb on the short arm of chromosome 11. The β globin gene cluster is under the control of β locus control region (BLCR) a major regulatory element located approximately 5 to 20 kb upstream of the gene (*Olivieri, 1999*).

The β thalassemia is inherited as pathologic alleles of one or more globin genes located on chromosome 11. These lesions range from total deletion to point mutations

that affect every step in the pathway of globin gene expression, transcription, processing of mRNA precursor, translation of mRNA and post translation integrity of β polypeptide chain (*Forget, 2001*).

Over 200 mutations have been described in the thalassemia phenotype and they have been identified and classified as β^+ or β^0 depending on whether they reduce or abolish the production of β globin chains (*Honig, 2004*).

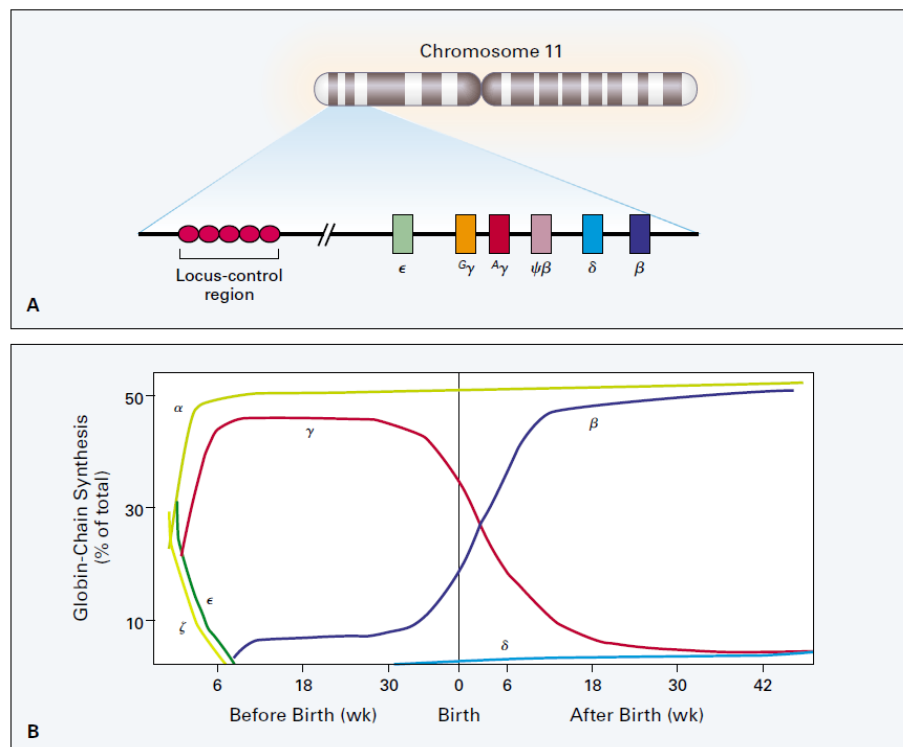


Figure (1): The β globin gene cluster. Panel A: The β globin like genes arranged in order in which they are expressed during development. Panel B: Shows the timing of normal development switching of human hemoglobin (*Olivieri, 1999*).

PATHOPHYSIOLOGY

The thalassemia syndromes were among the first genetic diseases to be understood at the molecular level. More than 200 β -globin and 30 α -globin mutation have been identified; these mutations result in decreased or absent productions of one globin chain (α or β) and a relative excess of the other. The resulting imbalance leads to unpaired globin chains which precipitate and cause premature death (apoptosis) of the red cell precursors within the marrow, termed ineffective erythropoiesis . Of the damaged but viable RBCs that are released from the bone marrow, many are removed by the spleen or hemolyzed directly in the circulation due to the hemoglobin precipitants. Combined RBCs destruction in the bone marrow, spleen and periphery causes anemia and, ultimately, an escalating cycle of pathology resulting in the clinical syndrome of severe thalassemia (*Kearney et al., 2007*).

Damaged erythrocytes enter the spleen and are trapped in this low pH and low oxygen environment; subsequent splenomegaly exacerbates the trapping of cells and worsens the anemia. Anemia and poor tissue oxygenation stimulate increased kidney erythropoietin production that further drives marrow erythropoiesis, resulting in increased ineffective marrow activity and the classic bony deformities associated with poorly managed TM and severe T1. Anemia in the severe thalassemia

phenotypes necessitates multiple RBC transfusions and, over time, without proper chelation, results in transfusion-associated iron absorption and can result in iron overload, even in untransfused patients who have TI (*Kearney et al., 2007*).

It has long been recognized that the severity of ineffective erythropoiesis affects the degree of iron loading, but until the recent discovery of hepcidin and understanding, its role in iron metabolism the link was not understood. Hepcidin; an antimicrobial hormone, is recognized as playing a major role in iron deficiency and overload. Hepcidin initially was discovered due to its role in the etiology of anemia of chronic inflammation or chronic disease (*Weinstein et al., 2002*).

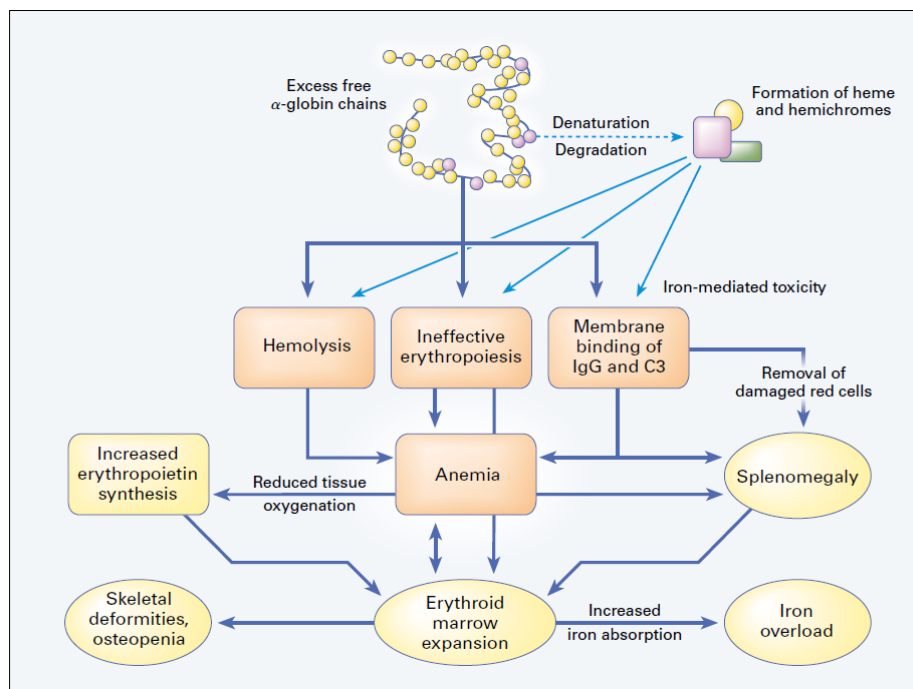


Figure (2): Effect of excess production of free α globin chains (*Olivieri, 1999*).

Clinical Picture of β -Thalassemia Major

The clinical picture of β -thalassemia major includes features that are due to the disease itself, as well as others that represent the consequences of therapy and are, in a sense, iatrogenic (*Caterina and Renzo, 2004*).

1. Anemia

Hypochromic microcytic anemia becomes apparent 3-6 months after birth when the switch from gamma to beta chain production should take place (*Honig, 2000*).

2. Iron overload

The primary long-term complication of chronic RBCs transfusions for thalassemia is iron loading and the resultant parenchymal toxicity. As iron levels build up in the body, transferrin becomes saturated. Iron begins to accumulate in the tissues, bound to protein storage molecules ferritin and haemosiderin. In iron overload, the capacity to bind iron is exceeded both within the cells and in the plasma compartment. Unbound iron or "free iron" begins to circulate. This is highly reactive and alternates between the ferrous (Fe^2) and ferric (Fe^3) forms. This results in gain and loss of electrons which can generate harmful free radicals (*Borgana-Pignatti, 2005*).

3. Skeletal changes:

Un-transfused or poorly transfused patients develop typical bone abnormalities that are due to extremely increased erythropoiesis with consequent expansion of the bone marrow to 15-30 times normal. The most striking skeletal changes are seen in the skull and facial bones. There is bossing of the skull and overgrowth of the maxillary region, the whole face gradually assumes a mongloid appearance (**Honig, 2000**). The outer and inner tables are thin, and the trabeculae are arranged in vertical striations, resulting in a "hair-on-end" appearance. A peculiar, stratified appearance of the skull has been reported. Ear impairment due to extramedullary marrow growing in the middle ear and progressive visual loss caused by compressive optic neuropathy have been reported (**Aarabi et al., 1998**).

Osteoporosis in thalassemia has been found to affect 51% of the patients, with an additional 45% affected by osteopenia. Fractures and bone pain of varying severity are common complaints among adult patients and they have been attributed to expanded bone marrow with consequent pressure on the cortical bone (**Angastiniotis et al., 1998**).

4. Liver and gall bladder:

El Alfy et al., **2004** stated that during the last years, liver disease has emerged as a major cause of morbidity in

patients with β -thalassemia major (BTM). In spite of its clinical relevance, β TM-associated liver damage has been insufficiently characterized. The liver is one of the major storage sites of iron, measurement of the liver iron content (LIC) had been described as the "gold standard" for the monitoring of body iron load and for assessing the risk of iron toxicity. Modern transfusion practices in the last decade and compliance to chelation therapy are the mainstay for prevention of liver cirrhosis.

Gallstones have been reported in 4 to 23% of patients with thalassemia. The large variability may be related to differences in transfusion practices and consequent variations in ineffective erythropoiesis and hemolysis, to the time of splenectomy and, probably more importantly, to the associated presence of the (TA) 7 promoter mutation of the uridine diphosphate-glucuronosyl transferase gene, which is associated with Gilbert syndrome (*Galanello et al., 2001*). Intercurrent episodes of hepatitis may lead to marked liver dysfunction and contribute to development of fibrosis and cirrhosis (*Masera et al., 1980*).

5. Splenomegaly and hypersplenism:

Progressive hepatosplenomegaly is a constant finding in homozygous β -thalassaemia. There is some evidence that children maintained on a high transfusion regimen develop less marked splenomegaly. However; when

children are maintained on inadequate transfusion, progressive enlargement of the spleen is the rule. Splenic enlargement may produce a variety of complications (*Oliveri, 1994*). There may be physical discomfort due to the size of the spleen. The formed elements of the blood may be trapped in the spleen producing anemia, thrombocytopenia and some degree of neutropenia. Trapped red cells in the splenic pool may account for 9 to 40% of the total red cell mass. Certainly in any patient with β -thalassaemia in whom there is splenomegaly with either increasing transfusion requirement or pancytopenia- the diagnosis of hypersplenism should be considered (*Olivieri, 1997*).

6. Renal Complications:

Kidney involvement is related to the patient's age, severity of anemia, frequency of blood transfusion and the type of anemia. DFX has also been reported to cause renal dysfunction in these patients. Several studies have shown proximal tubular damage and tubular dysfunction with beta thalassemia major (*Aldudak et al., 2000*).

7. Thrombotic Complications:

In recent years, there have been numerous reports of, thromboembolic complications in thalassemia. In a multicenter study the frequency of thromboembolic events was found to be 4% in patients with thalassemia major and

10% in patient with thalassemia intermedia (*Borgna-Pignatti et al., 1998*). A chronic hypercoagulable state has been observed even in childhood (*Eldor et al., 1999*). Concomitant prothrombotic conditions are frequently present in thalassemia patients after the first decade of life: insulin dependent diabetes, estrogen therapy, atrial fibrillation, and postsplenectomy thrombocytosis (*Eldor and Rachmilewitz, 2002*).

8. Pulmonary Complications:

Iron deposition in the lungs leads to elevation of pulmonary vascular resistance causing pulmonary hypertension and hypoxaemia, so chelation therapy reduces iron deposition and its contribution to the elevation of pulmonary vascular resistance (*Atichartakan et al., 2003*). Some studies showed mild to moderate small airway obstruction and air trapping by thin-section CT (*Khong et al., 2003*).

9. Pseudoxanthoma Elasticum:

The development of clinical and histopathologic manifestations of a diffuse elastic tissue defect, resembling inherited pseudoxanthoma elasticum, has been encountered with a notable frequency in patients with β -thalassemia. This clinical syndrome consisting of skin, ocular, and vascular manifestations, has a variable severity and is age dependent, with an onset usually after the second decade of