INTRODUCTION

Beta-thalassemia represents a group of recessively inherited haemoglobin disorders, first described by Cooley and Lee ***(Cooley and Lee, 1925)*** characterized by reduced synthesis of β-globin chains leading to synthesis of haemoglobin with an impaired oxygen binding capacity ***(Cooley and Lee, 1925)*.**

The homozygous state, known as beta-thalassemia major, results in a severe haemolyticanaemia requiring regular blood transfusions ***(Saka et al., 1995).***

Advent of safe transfusions with adjuvant chelation therapy has dramatically extended the life expectancy of thalassemic patients, who can now survive into their fourth and fifth decades of life ***(Saka et al., 1995).***

Clinical presentation of thalassemia major occurs between 6 and 24 months. Affected infants fail to thrive and become progressively pale. Feeding problems, and progressive enlargement of the abdomen caused by spleen and liver enlargement may occur ***(Thalassemia International Federation, 2008).***

If a regular transfusion program that maintains a minimum Haemoglobin (Hb) concentration of 9.5 to 10.5 g/dL is initiated, growth and development tends to be normal up to 10 to12 years. However, frequent blood transfusions have been

associated with serum iron overload, which may resultin hypogonadism, diabetes mellitus, hypothyroidism, hypoparathyroidism and other endocrine abnormalities ***(Pignatti et al., 2005).***

Hypogonadism was the most frequent endocrinopathy and affected both genders in picture of delayed puberty, delayed age of menarche in females to 17 years and azoospermia or asthenospermia in males ***(Viprakasit et al., 2001).***

Growth hormone deficiency was the second most frequent endocrinopathy, Growth retardation is frequently profound in these children ***(Singhal et al., 2014).***

The adolescent growth spurt is often delayed, even in children who are hyper-transfused, unless intensive iron chelation therapy is instituted early in life ***(Singhal et al., 2014).***

Hypoparathyroidism is one of the most important endocrine complications of thalassemia major. There are two possible explanations for the occurrence of hypoparathyroidism in thalassemia major patients. The first and possibly the most important factor is the deposition of iron in parathyroid gland leading to gland dysfunction. Another factor may be suppression of parathyroid secretion induced by bone resorption resulting from increased hematopoiesis secondary to chronic anemia ***(Habeb et al., 2013).***

The neurological abnormalities in patients with hypoparathyroidism are mainly caused by hypocalcemia. Clinical manifestations of hypocalcemia consist of latent and manifest tetany, seizures, carpopedal spasms, laryngeal stridor, and paresthesia in the hands or in the region of the lips. These signs and symptoms are the result of nerve excitability and tonic contractions of muscles ***(Rubin and Bilezikian, 2008).***

Osteoporosis represents an important cause of morbidity in the thalassemic population. Although the main role is played by hypogonadism ***(Hahalis et al., 2011)*** and bone marrow expansion, hypoxia, the etiology of this bone disease is multifactorial (hormonal deficiency, bone marrow expansion, increased iron stores, desferrioxamine toxicity) ***(El-Nashar et al., 2017).***

In addition, calcium and vitamin D deficiency associated with hypoparathyroidism are also implicated in osteoporosis ***(El-Nashar et al., 2017).***

Even well transfused patients with normal gonadal function who are supplemented with calcium have low bone mass by dual energy x-ray absorptiometry (DEXA) ***(Mirhosseini et al., 2013)*** suggesting other factors are also involved.

One of the main challenges to the assessment of bone health in patients with Thalassemia is accurate interpretation of densitometry results.

Many patients with Thalassemia have height deficits, and delayed puberty and/or bone age ***(Mirhosseini et al., 2013)*** and DEXA underestimates bone mass density (BMD) in small patients compared to those who are of normal size for chronological age ***(Mirhosseini et al., 2013).***

Medical therapy for beta thalassemia primarily involves iron chelation. The objective of iron chelation is to avoid the complications of iron overload such as cardiac, hepatic dysfunction and endocrinal complications ***(Pennell et al., 2010).***

Currently, the main iron chelators available for clinical use are desferrioxamine (DFO), deferiprone (DFP) and deferasirox (DFX). DFO, which requires routine subcutaneous or intravenous injection on 5 to 7 days per week, is considered a standard treatment for iron overload during the past four decades ***(Taher et al., 2009).***

DFP, expected to be a great improve over DFO, has been licensed to treat patients who were inadequately treated with DFO in Asia and Europe since 1990s. Although DFP has good compliance, some serious side effects such as gastrointestinal disturbances, arthropathy, neutropenia and agranulocytosis were reported. However, the combination of DFP and DFO, regarded as "shuttle hypothesis", was hoped to have a synergistic effect on iron removal and patient compliance ***(Uygun and Kurtoglu, 2013).***

Deferasirox (EXJADE) is preferred by patients due to its convenient once-daily oral administration and its cost-effectiveness ***(Waheed et al., 2014).*** Deferasirox has been approved by the FDA. Its use has also been studied in non-transfusion dependent thalassemia and both at low and high iron burdens ***(Uygun and Kurtoglu, 2013).***

AIM OF THE WORK

The aim of this study was to determine the prevalence of hypoparathyroidism in a group of patients with B-thalassemia major in relation to iron chelation therapy they received.

BETA THALASSEMIA

The thalassemias are a group of congenital anemia that have in common deficient synthesis of one or more of the globin subunits of the normal human hemoglobins. The primary feature is a quantitative one, but it is now clear that some of the thalassemias derive from structural hemoglobin variants leading to the production of an unstable globin chain. The thalassaemias are the commonest single-gene disorder ***(Lokeshwar et al., 2006).***

The thalassemias constitute a major public health problem in the countries surrounding the Mediterranean Sea and in the middle and Far East. Lack of standard medical care and of regular and safe blood supply in some countries is associated with considerable morbidity and mortality from thalassemias ***(Galanello and Origa, 2010)***.

β-thalassemia is prevalent in Mediterranean countries, the Middle East, Central Asia, India, Southern China, and the Far East as well as countries along the north coast of Africa and in South America. The highest carrier frequency is reported in Cyprus (14%), Sardinia (10.3%), and Southeast Asia ***(Wetherall and Clegg, 2001).***

It has been estimated that about 1.5% of the global population (80 to 90 million people) are carriers of β-thalassemia, with about 60,000 symptomatic individuals born

annually, the great majority in the developing world. However, accurate data on carrier rates in many populations are lacking, particularly in areas of the world known or expected to be heavily affected ***(Vichinsky et al., 2005).***

In Egypt β-thalassemia is the most common chronic hemolytic anemia (85.1%). A carrier rate of 9-10.2% has been estimated in 1000 normal random subjects from different geographical areas of Egypt ***(El-Beshlawy et al., 1999).***

Classification:

The β-thalassemias can be classified at different levels. Clinically, it is useful to divide them into three groups: the severe transfusion-dependent (major) varieties; the symptomless carrier states (minor) varieties; and a group of conditions of intermediate severity that fall under the loose heading "thalassemia intermedia". This classification is retained because it has implications for both diagnosis and management ***(Thalassemia International Federation, 2008).***

Thalassemias can also be classified at the genetic level into β0-thalassemia where no globin chain is synthesized at all, and hence they are called β0-thalassemia, whereas in others some globin chain is produced but at a reduced rate; these are designated β+-thalassemia ***(Higgs and Weatherall, 2009).***

Because the β-thalassemia occurs in populations in which structural hemoglobin variants are also common, it is not

unusual to inherit a β-thalassemia gene from one parent and a gene for a structural variant from the other. Furthermore, since both α and β-thalassemia occur commonly in some countries, individuals may receive genes for both types. All these different interactions produce an extremely complex and clinically diverse family of genetic disorders, which range in severity from death in utero to extremely mild, symptomless, hypochromic anemias ***(Higgs and Weatherall, 2009).***

Despite their genetic complexity, most thalassemias are inherited in a mendelian recessive or codominant fashion. Heterozygotes are usually symptomless, while more severely affected patients are either homozygous for α-or β-thalassemia, or compound heterozygous for different molecular forms of the disease ***(Steinberg et al., 2009).***

Molecular pathology:

β-globin is encoded by a structural gene found in a cluster with the other β-like genes spanning 70 Kb on the short arm of chromosome 11 (11p15.4). The genomic sequence spans 1600 bp and codes for 146 amino acids; the transcribed region is contained in three exons separated by two introns or intervening sequences (IVS). More than 200 mutations have been reported; the large majority are point mutations in functionally important regions of the β-globin gene. Deletions of the β-globin gene are uncommon ***(Joly et al., 2009).***

Cellular pathology:

The reduced amount (β+) or absence (β0) of β-globin chains result in a relative excess of unbound α- globin chains that precipitate in erythroid precursors in the bone marrow, leading to their premature death and hence to ineffective erythropoiesis. The degree of globin chain reduction is determined by the nature of the mutation at the β-globin gene located on chromosome 11 ***(Cohen et al., 2004).***

Peripheral hemolysis contributing to anemia is less prominent in thalassemia major than in thalassemia intermedia, and occurs when insoluble α-globin chains induce membrane damage to the peripheral erythrocytes. Anemia stimulates the production of erythropoietin with consequent intensive but ineffective expansion of the bone marrow (up 25 to 30 times normal), which in turn causes the typical bone deformities. Prolonged and severe anemia and increased erythropoietic drive also result in hepatosplenomegaly and extramedullary erythropoiesis ***(Cohen et al., 2004).***

Pathogenesis:

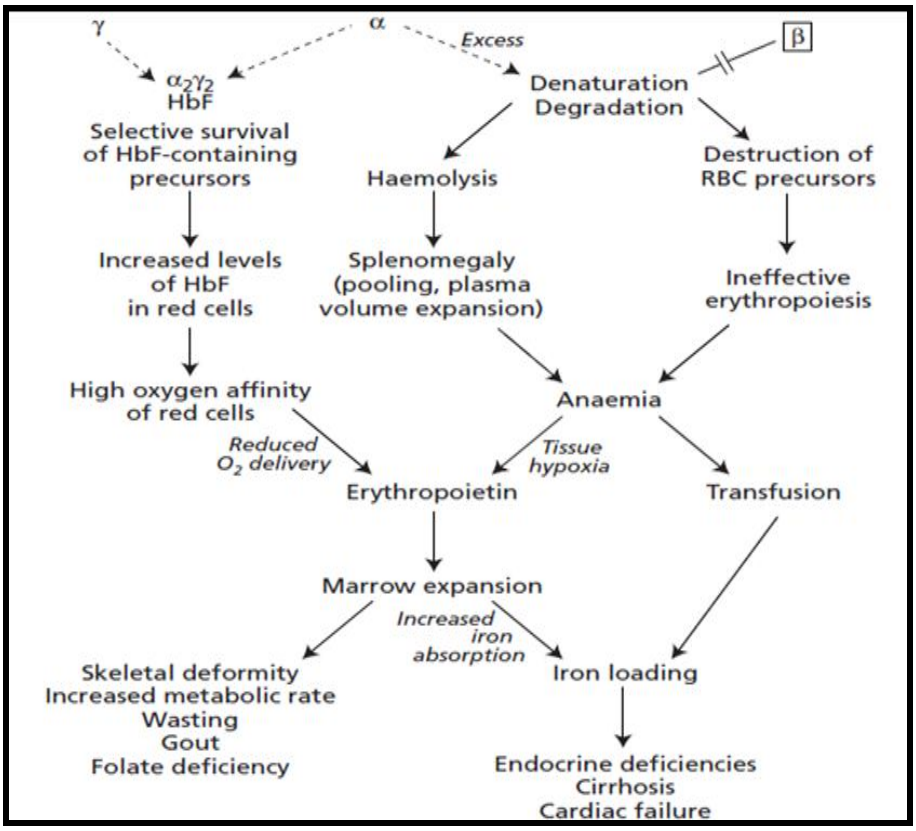

Figure (1): The pathophysiology of β-thalassemia ***(Cohen et al., 2004).***

1) Anemia:

Normal adult Hb is formed of two α- and two β-globin chains and heme. In β-thalassemia the underlying genetic defect is responsible for the inability of the erythroid cells to synthesize adequate amounts of β-globin chains. This causes excessive accumulation of free α-chains since there are no complementary β-chains to form a tetramer. The unbound α-chains precipitate within erythroblasts and red cells. These α-chain inclusions damage the cell membrane leading to the lysis of erythroblasts

and red cells in the bone marrow (ineffective erythropoeisis) ***(Thalassemia International Federation, 2008).***

The red cells containing α-chain aggregates have reduced flexibility and are trapped in the spleen. Removal of the inclusions by the splenic macrophages damages the red cell membranes; such red cells are ultimately destroyed by the macrophages in the spleen and liver. Thus, in addition to intramedullary destruction, red cells are also destroyed peripherally in the spleen (hemolysis) ***(Kazazian, 2002).***

Reduced synthesis of hemoglobin due to lack of β-globin production leads to the formation of microcytic hypochromic cells. Excessive peripheral destruction of red cells invariably leads to splenomegaly. Pooling of considerable proportion of red cells within large spleen further aggrevates the anemia. HbF is the predominant Hb in β-thalassemia major and is due to increased proliferation of cells capable of synthesizing γ-chains. HbF does not release oxygen as readily to the tissues as HbA since it poorly binds to 2,3diphosphoglycerate and thus exacerbates tissue hypoxia ***(Kazazian, 2002).***

2) Skeletal changes:

Severe anemia and tissue hypoxia stimulates erythropoietic drive and cause extreme bone marrow hyperplasia. Expansion of hyperactive bone marrow causes weakening and deformities of skull and facial bones. Thinning of cortex will lead to pathological fractures ***(Dhaliwal et al., 2004).***

3) Iron overload:

Iron absorption from the intestine is increased in thalassemia major due to ineffective erythropoiesis. Chronic regular blood transfusion therapy markedly increases the iron accumulation and causes iron overload. Iron overload damages parenchymal cells of various organs such as heart (arrhythmias and heart failure)**,** pancreas (diabetes mellitus), liver (cirrhosis) and gonads (infertility) ***(Angelucci et al., 2008).***

Malfunctions of the hepcidin-ferroportin axis contribute to the etiology of iron overload seen in thalassemia. Improvement and availability of hepcidin assays facilitates diagnosis of such conditions. The development of hepcidin agonists and antagonists may enhance the treatment of such anemias ***(Nemeth, 2010).***

Clinical features of Beta- thalassemia:

The phenotypes of homozygous or genetic compound heterozygous β-thalassemias include thalassemia major and thalassemia intermedia. Individuals with thalassemia major usually come to medical attention within the first two years of life and require regular RBC transfusions to survive. Thalassemia intermedia includes 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 (Table 1) ***(Thalassemia International Federation, 2008).***

Table (1): Prototypical forms of β-thalassemia ***(Olivieri, 1999).***

Variant	Chromosome 11	Signs and Symptoms
β-thalassemia trait	One gene defect	Asymptomatic
β-thalassemia intermedia	Two genes defective (mild to moderate decrease in β-globin synthesis)	Variable degrees of severity of symptoms of thalassemia major
β-thalassemia major	Two genes defective (severe decrease in β-globin synthesis)	Abdominal swelling, growth retardation, irritability, jaundice, pallor, skeletal abnormalities, splenomegaly; requires lifelong blood transfusions

β-Thalassemia major:

Clinical presentation of thalassemia major occurs between 6 and 24 months. Affected infants fail to thrive and become progressively pale. Feeding problems, diarrhea, irritability, recurrent bouts of fever, progressive enlargement of the abdomen caused by spleen and liver enlargement may occur and skeletal changes resulting from expansion of the bone marrow. Skeletal changes include deformities in the long bones of the legs and typical craniofacial changes (bossing of the skull, prominent malar eminence, depression of the bridge of the nose, tendency to a mongoloid slant of the eye, and hypertrophy of the maxillae, which tends to expose the upper teeth) ***(Thalassemia International Federation, 2008).***

If a regular transfusion program that maintains a minimum Hb concentration of 9.5 to 10.5 g/dL is initiated, growth and development tends to be normal up to 10 to 12 years ***(Thalassemia International Federation, 2008).***

Transfused patients may develop complications related to iron overload. Complications of iron overload in children include growth retardation and failure or delay of sexual maturation. Later iron overload-related complications include involvement of the heart (dilated myocardiopathy or rarely arrythmias), liver (fibrosis and cirrhosis), and endocrine glands (diabetes mellitus, hypogonadism and insufficiency of the parathyroid, thyroid, pituitary, and, less commonly, adrenal