Clinical Evaluation of Growth and Puberty in Relation to Thyroid Status and Iron Overload in Multitransfused Beta -Thalassemia Patients

Thesis

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ABSTRACT

Frequent blood transfusion has increased the life expectancy of patients with β-thalassemia major, but it causes progressive iron overload causing important oxidative damage, mostly to the heart, liver and endocrine glands. This study aims at clinical evaluation of growth and puberty in multitransfused Egyptian β-thalassemia patients and its relation to their thyroid hormones levels, serum ferritin level and chelation therapy. This cross sectional analytical study included 30 thalassemia major patients, aged 13 to 24 years, 16 (53.3%) were males and 14 (46.7%) were females, 22 patients (73.3%) were short, all patients hadn't attained full puberty, 71.4% of the girls >16years had primary amenorrhea, 63.3% of all patients had high TSH levels, 47.4% of them had low FT4 levels (clinical hypothyroidism) and the remaining patients(52.6%) had normal levels of FT4 (subclinical hypothyroidism). There were statistically signifiant inverse correlations between SD height and both serum ferritin and TSH (r= -0.90 & -0.906) and between Tanner score & both serm ferritin and TSH (r= -0.04 & -0.09) respectively. In this study, short stature, hypogonadism and hypothyroidism were frequent findings. These results support the need for vigilant clinical evaluation of growth and puberty, as well as appropriate hormonal evaluation in multitransfused thalassemic patients in order to detect and treat endocrine dysfunction early. It is also recommended to start aggressive and adequate chelation from early life so that permanent damage to the endocrine glands can be prevented.

Keywords : Multitransfused , thalassemia , hypogonadism , puberty , hypothyroidism

ABBREVIATONS

- **ABT:** Allogenic Blood Transfusion
- **ACTH:** Adrenocorticotrophic hormone
- **ANC:** Absolute neutrophil count
- **BMT:** Bone Marrow Transplantation
- **BPA:** Bisphenol A
- **CBC:** Complete blood picture
- **CDC:** Centers for Disease Control and Prevention
- **CT:** Computed Tomography
- **DFO:** Deferrioxamine
- **DFP:** Deferiprone (L1)
- **DFX:** Deferasirox
- **DHPLC:** Denaturing high performance liquid chromatography
- **DNA:** Deoxynucleic acid
- **DVT:** Deep venous thrombosis
- **ECG:** Electrocardiography
- **EPOs:** Erythropoeitins
- **FSH:** Follicle stimulating hormone
- **FT4:** Free thyroxine
- **GH:** Growth hormone
- **GH-IGF-1:** Growth hormone insulin-like growth factor-1
- **GIT:** Gastrointestinal tract
- **GnRH:** Gonadotropin-releasing hormone
- **GVHD:** Graft versus –host disease
- **Hb:** Haemoglobin
- **HbA:** Adult haemoglobin A
- **HbA_2:** Adult haemoglobin A_2
- **HbF:** Fetal hemoglobin
- **HBV:** Hepatitis B virus
- **HCC:** Hepatic cell carcinoma
- **hCG:** human Chorionic Gonadotrophin
- **HCV:** Hepatitis C virus
- **HIV:** Human Immunodeficiency virus
- **HLA:** Human leukocyte antigen

- **hMG :** human menopausal gonadotrophin
- **HU:** Hydroxyurea
- **ICSI:** Intracytoplasmatic sperm injection
- **IGF-1:** Insulin like - growth factor -1
- **L–carnitine:** Levo - carnitine
- **LFTS:** Liver function tests
- **LH:** Luteinizing hormone
- **LIC:** Liver iron concentration
- **MCH:** Mean corpuscular hemoglobin
- **MCV:** Mean corpuscular volume
- **MRI:** Magnetic Resonance Imaging
- **mRNA:** messenger riboneocleic acid
- **NO:** Nitric oxide
- **NTBI:** Non- transferrin bound iron
- **OPSI:** Overwhelming post splenectomy infection
- **OPSS:** Overwhelming post splenectomy sepsis
- **PCBs:** Polychlorinated biphenyl
- **PCR:** Polymerase chain reaction
- **PGD:** Preimplantation genetic diagnosis
- **RBCs:** Red blood cells
- **RDW:** Red blood cell distribution width
- **RES:** Reticuloendothelial system
- **rhGH:** recombinant growth hormone
- **SQUID:** Magnetic biosusceptometry
- **T4:** Thyroxine
- **TIBC:** Total iron binding capacity
- **TM:** Thalassaemia major
- **TRH:** Thyrotropin-releasing hormone
- **TSH:** Thyrotropin-stimulating hormone
- **TRIM:** Transfusion related immunomodulation
- **US:** Ultrasonography
- **WBCs:** White blood cells

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INTRODUCTION

Beta-thalassemia represents a group of recessively inherited hemoglobin disorders first described by Cooley and Lee (1925) and characterized by reduced synthesis of β-globin chain. The homozygous state results in severe anemia, which needs regular blood transfusion. Frequent blood transfusion combined with chelation therapy is just a supportive treatment for thalassemia major and leads to an improved rate of survival and dramatically extends the life expectancy of thalassemic patients who can now survive into their fourth and fifth decades of life ***(Shamshirsaz et al., 2003)***.

Frequent blood transfusion, which is critical for survival of thalassemic patients is a double-edged sword, prolonging life while eventually leading to iron overload, resulting in various complications including endocrine dysfunctions ***(Cunningham et al., 2004)***.

Iron deposits in the reticuloendothelial system, then enters the parenchyma, causing important oxidative damage, mostly to the heart, liver, and endocrine glands ***(Grundy et al., 1994)***. The amount of iron deposits has been the principal factor responsible for the clinical complications of the disease ***(Brittenham et al., 1994 , Delvecchio and Cavallo, 2010)*** .

Short stature and hypogonadism are extremely frequent in patients with thalassemia. Many factors are responsible for short stature in patients with thalassemia, the most important of which are dysfunction of the GH-IGF-I axis and desferoxamine (DFX)-induced bone dysplasia ***(Low Louis, 2005).***

Hypogonadism is one of the most frequent endocrine complications, mostly due to gonadotropin deficiency secondary to siderosis of the pituitary gland . The child

with thalassemia major has a particular growth pattern, which is relatively normal until age of 9 –10 years, after this age a slowing down of growth velocity and reduced or absent pubertal growth spurt are observed due to failure of hypothalamic – pituitary – gonadal axis. Sex steroid treatment for induction of puberty and /or maintenance of sexual characteristics is necessary ***(Raiola et al. 2003).***

Various authors have reported a high incidence of growth retardation, delayed puberty and endocrine dysfunction in polytransfused thalassemic patients ***(Aydinok et al., 2002; Lo and Singer, 2002).*** Researchers have documented evidence of hypothalamic - pituitary dysfunction, hypothyroidism, hypoparathyroidism, adrenal insufficiency, and diabetes mellitus in patients with β-thalassemia major **(*Gamberini et al.,1998 ; Gulati et al.,2000).***

AIM OF THE WORK

This study aims at clinical evaluation of growth and pubertal status in multitransfused Egyptian β- thalassemia patients and their relations to their thyroid hormones changes , serum ferritin level and chelation therapy.

CHAPTER I

Beta Thalassemia

• Historical Considerations:

The thalassemias are inherited disorders of hemoglobin (Hb) synthesis. Their clinical severity widely varies, ranging from asymptomatic to severe or even fatal entities. The name Mediterranean anemia which Whipple introduced, is misleading because the condition can be found in any part of the world ***(Galanello and Origa, 2010)***. In 1925, Thomas Cooley, a Detriot pediatrician, described a severe type of anemia in children of Italian origin. He noted abundant nucleated red blood cells (RBCs) in the peripheral blood, which he initially thought as erythroblastic anemia, an entity that Von Jaksh described earlier. Although Cooley was aware of the genetic nature of the disorder, he failed to investigate the apparently healthy parents of the affected children . In Europe, Riette described Italian children with unexplained mild hypochromic and microcytic anemia ***(Kuypers, 2008)***. In addition, Wintrobe and Coworkers in the United States reported a mild anemia in both parents of a child with Cooley anemia, this anemia was similar to the one that Riette described in Italy. Only then was Cooley's severe anemia recognized as the homozygous form of the mild hypochromic and microcytic anemia that Riette and Wintrobe described. This severe form was then labeled as thalassemia major and the mild form as thalassemia minor ***(Yaish, 2009)***. The first description in Egypt was by Professor El Diwany in 1944.Thalassemia represents the commonest cause of haemolytic anemia. The carrier rate in Egypt in many studies ranged from 9 to 10.2% ***(Habib and Book, 1982).***

- **Disease name and synonyms:**

The term thalassemia is derived from the Greek, thalassa (sea) and haima(blood). β-thalassemia includes three main forms: Thalassemia Major, variably referred to as "Cooley's Anemia" and "Mediterranean Anemia", Thalassemia Intermedia and Thalassemia Minor also called "β-thalassemia carrier", "β-thalassemia trait" or "heterozygous β-thalassemia". Apart from the rare dominant forms, subjects with thalassemia major are homozygotes or compound heterozygotes for β^0 or β^+ genes, subjects with thalassemia intermedia are mostly homozygotes or compound heterozygotes and subjects with thalassemia minor are mostly heterozygotes ***(Galanello and Origa, 2010)***.

- **Classification:**

The thalassemias are a group of inherited hematologic disorders, caused by defect in the synthesis of one or more of hemoglobin chains **(*Muncie and Campbell, 2009)* .** Beta-thalassemias are caused by point mutations or, more rarely, deletions in the β-globin gene on chromosome 11, leading to reduced (β^+) or absent (β^0) synthesis of the β chains of hemoglobin. β-thalassemias can be classified into:

- Beta-thalassemia

  •Thalassemia major
  •Thalassemia intermedia
  •Thalassemia minor

- Beta-thalassemia with associated Hb anomalies

  • HbC/Beta-thalassemia
  • HbE/Beta-thalassemia
  • HbS/Beta-thalassemia (clinical condition more similar to sickle cell disease than to thalassemia major or intermedia)

- Hereditary persistence of fetal Hb and beta-thalassemia
- Autosomal dominant forms
- Beta-thalassemia associated with other manifestations
    - Beta-thalassemia-tricothiodystrophy
    - X-linked thrombocytopenia with thalassemia ***(Galanello and Origa, 2010)***.

• Epidemiology:

Beta-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. The high gene frequency of beta-thalassemia in these regions is most likely related to the selective pressure from *Plasmodium falciparum* malaria ***(Flint et al., 1998)***. Population migration and intermarriage between different ethnic groups has introduced thalassemia in almost every country of the world, including Northern Europe where thalassemia was previously absent. 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 total annual incidence of symptomatic individuals is estimated at 1 in 100,000 throughout the world and 1 in 10,000 people in the European Union. However, accurate data on carrier rates in many populations are lacking ***(Vichinsky,2005)***. According to Thalassemia International Federation, only about 200,000 patients with thalassemia major are alive and registered as receiving regular treatment around the world. The most common combination of beta-thalassemia with abnormal Hb or structural Hb variant with thalassemic properties is HbE/β-thalassemia which is most prevalent in Southeast Asia where the carrier frequency is around 50% ***(Thalassemia International Federation, 2008)***.

Although β-thalassemia has more than 200 mutations, most are rare. Approximately 20 common alleles constitute 80% of the known thalassemia

worldwide, 3% of the world population carries genes for β-thalassemia, and in Southeast Asia, 5-10% of population carries genes for α-thalassemia. In a particular area there are fewer common alleles ***(DeBaun and Vichinsky, 2007).*** In Egypt β-thalassemia, is the most common genetic disorder, and is a major health problem with an estimated carrier rate of 9 – 10 %, it is second only to iron deficiency anemia ***(Hussein et al., 2007).***

• Pathophysiology:

The reduced amount (β^+) or absence (β^0) 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 ***(Galanello and Origa, 2010).***

Peripheral hemolysis contributing to anemia is more 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 ***(Fibach and Rachmilewitz , 2008 ; Galanello and Origa, 2010).***