INTRODUCTION

Pulmonary dysfunction is one of the least understood complications in patients with chronic hemolytic anemias, although it is not uncommon, having been reported in up to 80% of patients with the disease **(Eidani et al.,2009).**

Atopic manifestations are also reported in patients with chronic hemolytic anemias, affecting their clinical conditions and share in pulmonary dysfunction as regard respiratory manifestations and abnormal pulmonary function tests **(Boyd et al., 2009).**

Thalassemias *are* forms of inherited autosomal recessive blood disorders that originated in the Mediterranean region. In thalassemia, the disease is caused by the weakening and destruction of red blood cells. Thalassemia is caused by variant or missing genes that affect how the body makes hemoglobin. Hemoglobin is the protein in red blood cells that carries oxygen. People with thalassemia make less hemoglobin and fewer circulating red blood cells than normal, which results in mild or severe anemia **(Kong et al., 2004).**

Sickle cell disease (SCD) and its variants are genetic disorders resulting from the presence of a mutated form of hemoglobin, hemoglobin S (HbS). The most common form of SCD is homozygous HbS disease (Hb SS), an autosomal recessive

disorder first described by **Herrick** in 1910. SCD causes significant morbidity and mortality, particularly in people of African and Mediterranean ancestry. Morbidity, frequency of crisis, degree of anemia and the organ systems involved vary considerably from individual to individual **(Slavov et al., 2011).**

Bronchial Asthma is a chronic inflammatory disease of the airways characterized by airway hyper-responsiveness, inflammation and remodeling. Inhalation of allergen immediately induces the early asthmatic reaction (EAR) which involves cross-linking of IgE by allergen, followed by activation of cells bearing IgE receptor (predominantly mast cells and basophils) with subsequent release of cytokines, proteases, and proinflammatory mediators **(Monika et al., 2008).**

Spirometry assesses the integrated mechanical function of the lung, chest wall, and respiratory muscles by measuring the total volume of air exhaled from a full lung (total lung capacity [TLC]) to an empty lung (residual volume). Spirometry is used to establish baseline lung function, evaluate dyspnea, detect pulmonary disease, monitor effects of therapies used to treat respiratory disease, evaluate respiratory impairment, evaluate operative risk, and perform surveillance for occupational-related lung disease **(Castile et al., 2000).**

Immunoglobulin E (IgE) is a class of antibody (or immunoglobulin "isotype") that has been found only in mammals.

IgE's plays an essential role in type I hypersensitivity which manifests various allergic diseases, such as allergic asthma, allergic rhinitis, food allergy and some types of chronic urticaria and atopic dermatitis ***(*Watanabe et al., 2005*).***

IgE levels in a normal ("non-atopic") individual are only 0.05% of the Ig concentration compared to 10 mg/ml for the IgGs (the isotypes responsible for most of the classical adaptive immune response). It is capable of triggering the most powerful inflammation reactions **(Gould et al., 2003).**

AIM OF THE WORK

To study the pulmonary functions and atopic manifestations in multi-transfused chronic hemolytic anemia patients.

We also aim at finding out the relation between serum IgE level and spirometric pulmonary function tests in chronic hemolytic anemia patients.

THALASSEMIA

Historical Background:

Thalassemia consists of a group of inherited diseases of the blood. About 100, 000 babies worldwide are born with severe forms of the disease each year. Thalassemia occurs most frequently in people of Middle Eastern, Southern Asian, Italian, Greek, and African ancestry. β-Thalassemia usually becomes symptomatic as severe, progressive hemolytic anemia during 2nd six months of life. Regular blood transfusions are necessary in these patients to prevent the cardiac decompensation caused by anemia **(Eldor et al., 2002).**

Thomas Cooley and **Pearl Lee** first described homozygous β-Thalassemia in 1925. 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; Cooley et al., 1927 and Whipple et al., 1936).**

Recently, the molecular biology and genetics of the thalassemia syndrome have been described in details, revealing

wide range of mutations encountered in each type of thalassemia. ß-thalassemia alone can arise from more than 150 mutations **(Nathan et al., 2003).**

Distribution and Population at Risk:

Thalassemia is common in the Mediterranean, equatorial or near equatorial region of Asia and Africa. The thalassemia belt extends along the shores of the Mediterranean and throughout the Arabian peninsula, Turkey, Iran, India and Southeastern Asia, especially Thailand, Cambodia and Southern China. Gene frequencies in these regions range from 2.5 to 15% **(Hoffman et al., 1995).**

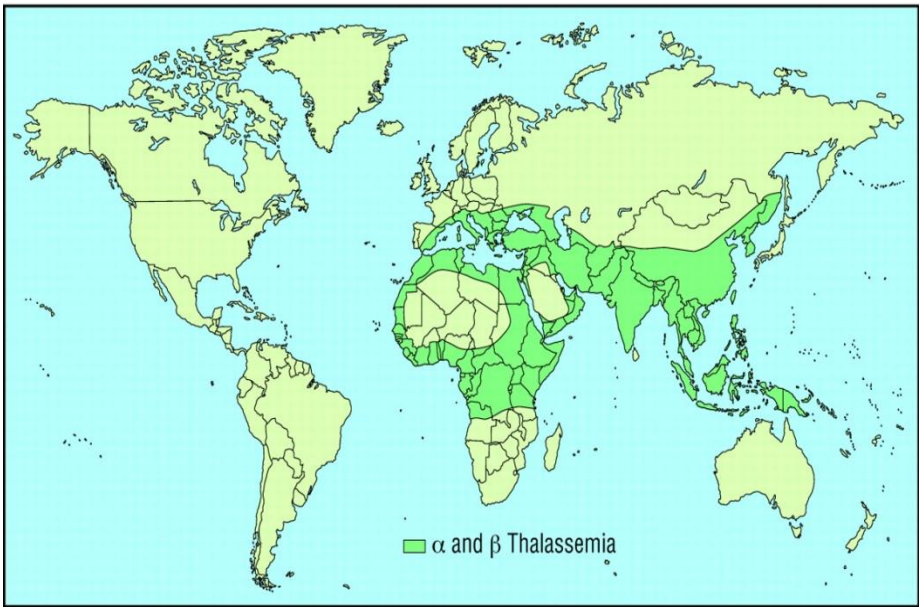

Fig. (1): Regions where thalassemia is endemic.
Quoted from **(Weatherall, 1997).**

Worldwide, about 60000 children with thalassemia major are born annually and about 150 million people carry thalassemia genes **(Cao et al., 2002).**

β-Thalassemia is the most frequent hemoglobinopathy in Egypt. The carrier rate of this disease varies between 5.3 and ≥ 9% and the gene frequency is 0.03, so it was estimated that 1, 000/1.5 million per year live birth born with thalassemia disease **(El-Beshlawy et al., 2007).**

Beta-thalassemia is a major health problem in Egypt. It has been estimated that of the 1.5 million live births. 1000 children with beta-thalassemia major are born annually. Although the available treatment has increased the life expectancy of patients, it is still unsatisfactory and represents a significant drain on the country's resources **(Khalifa AS et al.,1997).**

Normal Human Hemoglobin:

Genetics:

Hemoglobin is the oxygen-carrying moiety of erythrocytes. It is a polypeptide tetramer, globular in structure, and consisting of two pairs of unlike globin chains (i.e., α plus β, δ, or γ), which form

a shell around a central cavity containing four oxygen-binding heme groups each covalently linked to α globin chain. In healthy adults, 95% of the Hb is Hb A ($\alpha_2\beta_2$) with small amounts (3.5%) of Hb A_2 ($\alpha_2\delta_2$) and Hb F ($\alpha_2\gamma_2$) present. During embryonic development, "pre alpha" ξ globin chains contribute to embryonic Hb. During fetal development, β-like globin chains ε and γ contribute to the Hb **(Gwendolyn, 2000).**

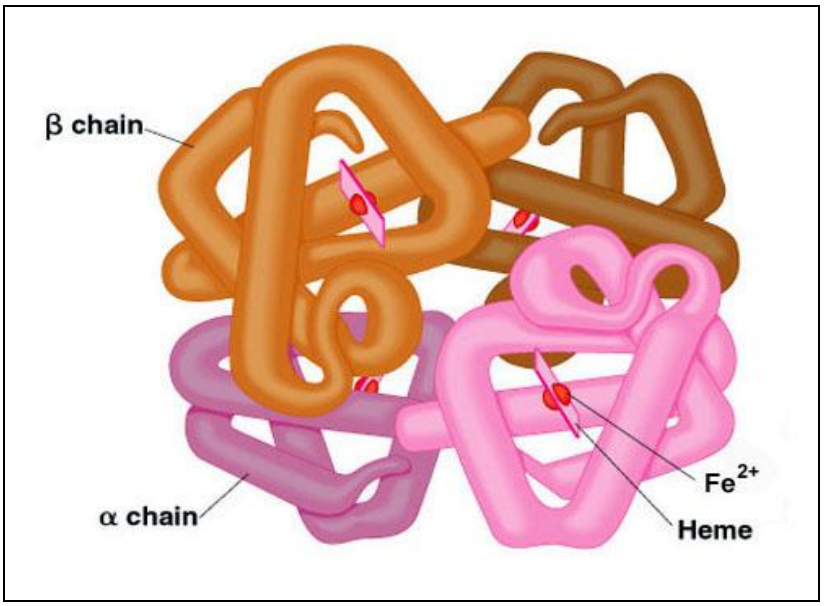

Fig. (2) Adult hemoglobin structure (2α chains and 2β chains) (**Nathan 2005**).

Embryonic Hemoglobins:

The blood of early human embryos contains two slowly migrating hemoglobins, Gower-1, Gower-2, and Hb Portland, which has HbF-like mobility.

Hb Gower-1 has structure ζ2ε2 and Gower-2 has α2ε2. Hb Portland has structure ζ2γ2. In embryos of 4-8 wk gestation, the Gower hemoglobins predominate, but by 3rd month they have disappeared **(Stamatoyannopoulos et al., 2001).**

- Fetal Hb:

Hb F contains γ polypeptide chains in place of the β-chains of HbA. After 8th gestational wk, HbF is the predominant hemoglobin; at 24th wk of gestation it constitutes 90% of the total hemoglobin. During the 3rd trimester, a gradual decline occurs, so that at birth HbF averages 70% of the total. Synthesis of HbF decreases rapidly postnatally, and by 6-12 months of age only a trace is present **(Cohen et al., 2004).**

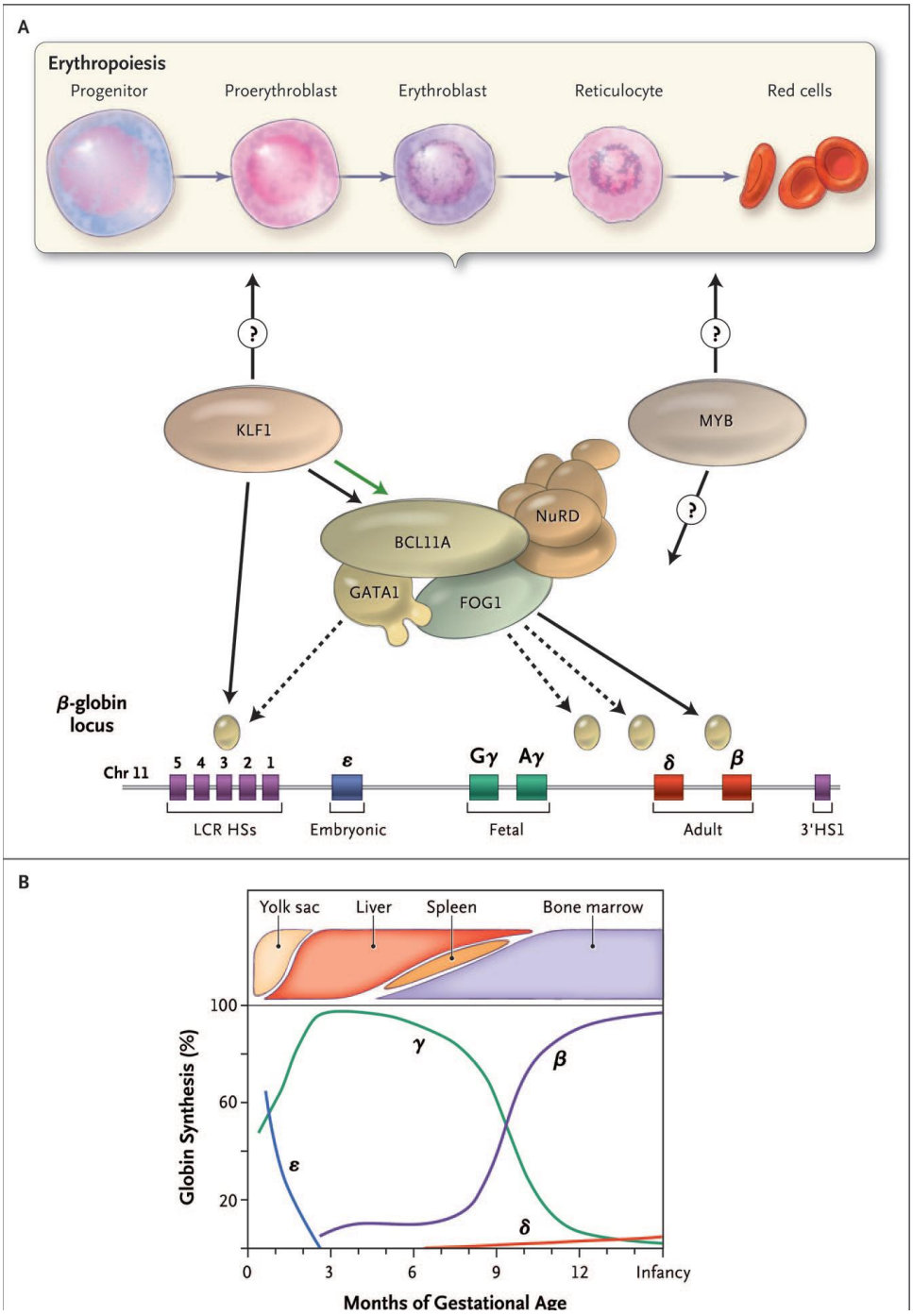

Fig. (3): β-Globin synthesis at various stages of embryonic and fetal development **(Nathan et al., 2005).**

- Adult Hb:

Some Hb (α2, β2) can be detected in even the smallest embryo. Accordingly, it is possible as early as 16-20 weeks gestation to make a prenatal diagnosis a major β-chain hemoglobinopathies, such as thalassemia major **(Inati et al., 2006).**

Classification of Thalassemia:

Table (1): Clinical and hematological features of the principle forms of thalassemia ***(Robin et al., 2008).***

Type of Thalassemia	Globin genotype	Hematologic features	Clinical expression	Hemoglobin findings
β –thalassemia β –homozygous	β-/ β -	Sever anemia Normoblastemia	Cooley's anemia	HBF>90% NO HbA, HbA2
β +homozygous	β +/ β +	Anisocytosis moderately severe anemia	Thalassemia intermedia	HbA, 20%-40% HbF 60%-80%
β heterozygous	β / β -	Microcytosis hypochromia, mild to moderate anemia	May have splenomegaly, jaundice	Increased HbA2 And HbF
β heterozygous	β / β +	Microcytosis hypochromia, mild to anemia	Normal	Increased HbA2 And HbF
β -silent carrier, heterozygous	β / β +	Normal	Normal	Normal
δβ - heterozygous	δβ / (δβ)-	Microcytosis hypochromia, mild to moderate anemia	Usually normal	HbF 5%-2% HbA2 normal or low
γδβ - heterozygous	γδβ/ (γδ β)-	Newborn: Microcytosis, Hemolytic anemia, Normoblastemia, Adult similar to heterozygous δβ	Newborn: Hemolytic disease with splenomegaly. Adult similar to heterozygous δβ	Normal
α-thalassemia α -silent carrier α –trait	-α/α, α α, α/α, α -, α/-, α -, -/α, α	Mild microcytosis or normal microcytosis hypochromia, mild anemia	Normal Usually normal	Newborn: Hb Bart's 5%- 10% Child or adult: Normal
HbH disease	-, α/-, -	Microcytosis, inclusion bodies by supravital staining, moderately severe anemia	Thalassemia Intermedia	Newborn: Hb Bart's20%-30% Child or adult: HbH 4%-20%
α - hydrops fetalis	-, -/-, -	Anisocytosis, pokliocytosis, severe anemia	Hydrops fetalis: Usually stillborn or neonatal death	Hb Bart's (γ4) 80%- 90%, no HbA or HbF

Beta thalassemia

In contrast to α-thalassemia most of β-thalassemia syndromes are caused by mutations affecting gene regulation or expression rather than gene deletion **(Honig et al., 2004).**

This disease represents the homozygous state of autosomal recessive gene for which the heterozygous state associated with much milder hematological changes, the severe homozygous conditions known as thalassemia major, where the heterozygous state were designated according to their severity as thalassemia minor or later the term thalassemia intermedia was used to describe disorders of milder form **(Nathan et al., 2005).**

Several clinical forms of beta thalassemia are recognized; some of the more common ones are listed:

- Silent carrier beta thalassemia: Similar to patients who are alpha thalassemia silent carriers, these patients have no symptoms except for possible low red blood cells indices. The mutation causing the thalassemia is very mild **(Weatherall et al., 2000).**

- Beta thalassemia trait: patients have mild anemia, abnormal red cell indices, and abnormal Hb electrophoresis with elevation of Hb A2, Hb F or both. Peripheral blood film examination usually reveals marked hypochromia and microcytosis (without the anisocytosis usually encountered in iron deficiency anemia), target cells and faint basophilic stippling. The

production of beta chains from the abnormal allele varies from complete absence to variable degrees of deficiency **(Hassan et al., 2001).**

- Thalassemia intermedia: This condition is due to a compound homozygous state, resulting in anemia of intermediate severity, which typically does not require regular blood transfusions **(Hassan et al., 2001).**

  β-Thalassemia intermedia patients had a higher incidence of left atrium dilatation, right ventricular dilatation and pulmonary hypertension, Administration of hydroxyurea (HU) alone was associated with significant improvement in hematological parameters and quality of life for β-TI patients **(Mokhtar GM et al.,2011).**

- Beta thalassemia associated with beta chain structural variants: The most significant condition in this group of thalassemia syndromes is the Hb E/beta thalassemia, which may vary in it's clinical severity from as mild as thalassemia intermedia to as severe as beta thalassemia major **(Hassan et al., 2001).**

- Beta thalassemia major: The inheritance of 2β globin gene deletion leads to lack of adequate production of the β globins. In general, they present between 8 and 10 months of life when fetal hemoglobin production decreases and adult hemoglobin production ensues, the impaired β globin production leads to an excess of α globins which form unstable tetramers and leads to hemolytic anemia **(Olivieri et al., 1999).**

Pathophysiology:

More than 200 disease-causing mutations have been described to date. The large majority of mutations are simple nucleotide substitutions or deletions or insertions of oligonucleotides leading to frame shift. Rarely β-thalassemia is the result of gross gene deletions **(Weatherall & Clegg, 2001).**

The major cellular pathogenic mechanisms are based primarily on the deleterious effects produced by the accumulation of the excess α-globin chain in beta thalassemia. Indeed, studies on the synthesis of alpha and beta globin proved that the extent of mismatch determines the severity of the anemia in both alpha and beta thalassemia **(Schrier, 2002)**.

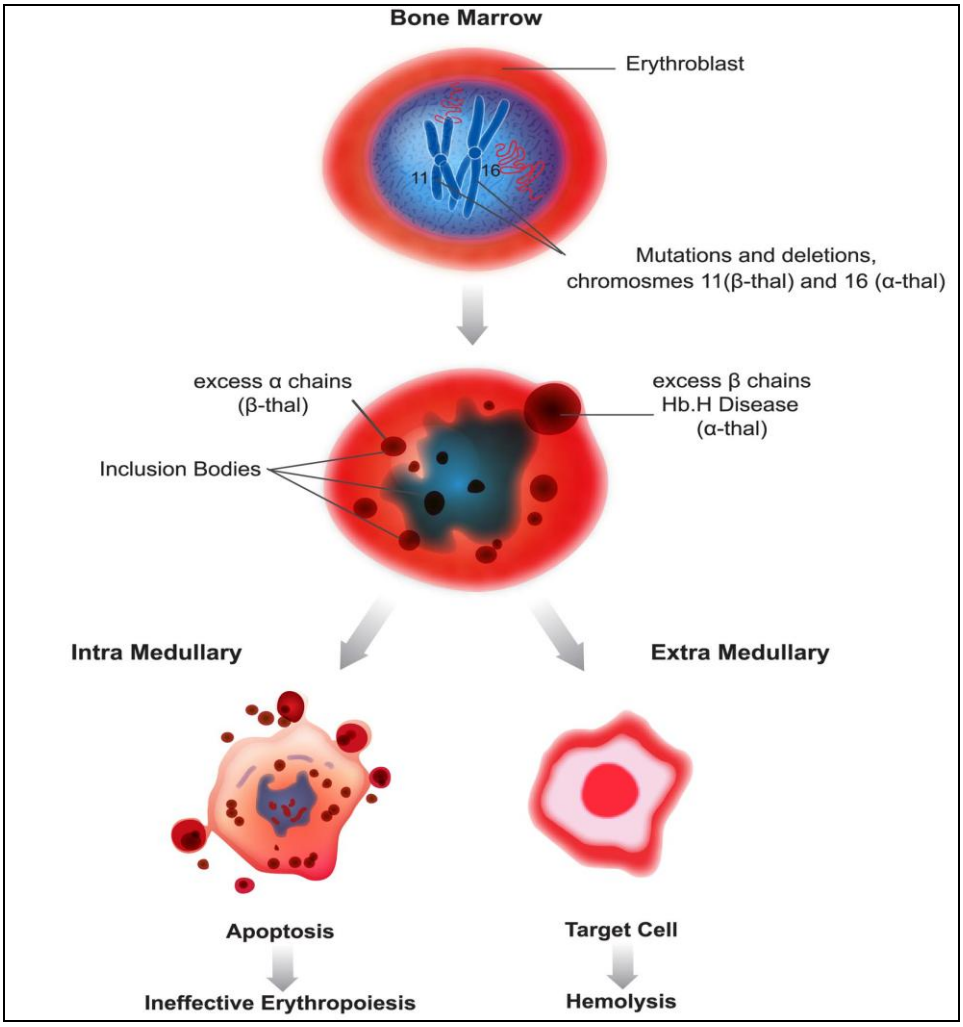

Fig. (4): Mechanism of ineffective erythropoiesis and hemolysis in thalassemia **(Giardine, 2011).**

Disease severity in patients with β-thalassemia varies greatly and patients are usually classified into Thalassemia Major (TM) or Intermedia according to clinical criteria. The requirement for at least 8 transfusions a year before the age of four years is often used to distinguish the 2 types of the disease **(Modell et al., 2008; Thuret et al., 2010).**