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Introductory Chapter: Thalassemia - An Overview

Isam Jaber Al-Zwaini

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1. Introduction

Thalassemias are a heterogenous group of genetic disorders, transmitted as autosomal recessive inheritance, in which the rate of hemoglobin production is partially or completely suppressed due to the reduced rate of synthesis of α - or β -chain, the two chains of adult hemoglobin (Hb A) [1]. The molecular defects that cause thalassemia are located within the human globulin gene which encodes for alpha and beta globulin polypeptide chain of hemoglobin on chromosome numbers 16 and 11, respectively. These genetic molecular defects in thalassemia lead to reduced or no production of one globulin chain with the excess of the other resulting in alpha thalassemia when the alpha chain is affected and beta thalassemia when the beta chain is affected [2]. In thalassemia, the imbalance of globin chain synthesis leads to red cell damage resulting in destruction of red cells in the marrow (ineffective erythropoiesis) and peripheral circulation (hemolysis) [3]. In addition to pediatrician and hematologist, family physician and general practitioner need to know what thalassemia is, how it is diagnosed and differentiated from other hypochromic microcytic anemias, and what are the principles of treatment and prevention.

2. Epidemiology

Classically, thalassemia affecting population across thalassemic built which extends from the Mediterranean region through Middle East and Sub-Saharan Africa to South and Southeast Asian countries. Nowadays, thalassemia occurs all over the world because of continual migrations of population from these areas to western countries. Thalassemia affects both sexes equally, occurring approximately in 4.4% of every 10,000-live birth [4] and accounting for about 60,000–70,000 children each year who born with different types of thalassemia [5].

3. Genetic bases and hemoglobin types

In the embryonic life, blood in the blood islands of the yolk sac produces specific types of hemoglobin called Gower 1 composed of two zeta chains and two epsilon chain ($\zeta_2\epsilon_2$), Gower 2 composed of two alpha chains and two epsilon chains ($\alpha_2\epsilon_2$), and Portland hemoglobin composed of two zeta chains and two gamma chains ($\zeta_2\gamma_2$). In the first trimester, definitive hematopoietic stem cell emerges from the ventral wall of the dorsal aorta which then migrates to fetal liver where fetal hemoglobin is produced (Hb F). Around the time of birth, hematopoietic stem cell migrates to the bone marrow which will become the main site of adult hemoglobin production for the rest of life. The switching from embryonic to fetal and then to adult hemoglobin occurs as a result of well-coordinated developmental stage due to specific expression of globin genes in Alpha and Beta globin loci [6]. Each type of hemoglobin composes of four globin chains. Fetal hemoglobin has two alpha and two gamma chains ($\alpha_2\gamma_2$) accounting for approximately 80% of hemoglobin at birth, while adult hemoglobin (Hb A1) has two alpha and two beta chains ($\alpha_2\beta_2$) constituting the remaining 20%. While the

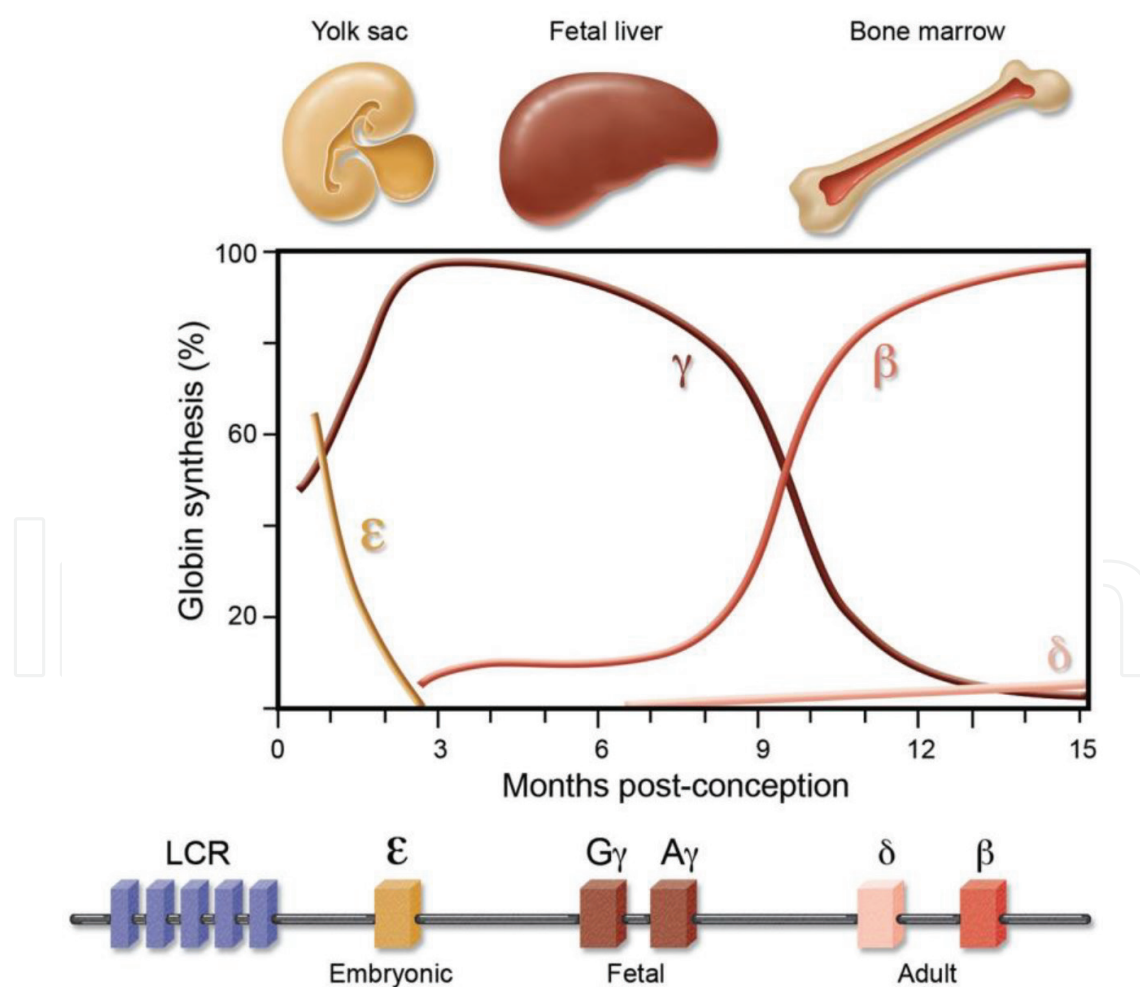


Figure 1. Embryonic, fetal, and adult hemoglobin [7].

switch on transition from gamma chain to beta chain production after birth, the hemoglobin A1 gradually replaces hemoglobin F, and at 6 months of age, Hb A1 constitutes about 97% and Hb F about 1%. The remaining small amount is of Hb A2 composed of two alpha and two delta chains ($\alpha_2\delta_2$) (**Figure 1**).

In alpha thalassemia, reduced or no production of alpha globin chains is usually caused by deletion of one or more of the genes responsible for its production. Deletion of one gene results in alpha thalassemia carrier state in which the patient is asymptomatic with normal hematological findings. Deletion of two genes results in alpha thalassemia trait or alpha thalassemia minor in which the patient has no or very mild anemia but with microcytosis. On the other hand, deletion of three genes results in significant production of hemoglobin H consisting of four beta chain (β_4), also called alpha thalassemia intermedia, which usually presents with hemolysis, microcytosis, and splenomegaly, while the deletion of the four genes results in the production of significant amount of hemoglobin Bart which consists of four gamma chain (γ_4); Bart's hemoglobin, also called alpha thalassemia major, definitely will result in hydrops fetalis.

Regarding the more common type of thalassemia, B thalassemia, more than 200 mutations, and rarely deletions, of the two genes responsible for the production of B chain can be crimi-nated. In B thalassemia, the production of beta chain can range from normal to completely absent resulting in variable clinical presentations. In the one-gene defect, the patient has thalassemia minor, also called trait, in which the patient is asymptomatic apart from mild anemia (hemoglobin level is 2–3 g below the average of his age) and microcytosis. This is commonly mistaken as the more common iron deficiency anemia. If both genes are affected resulting in no or reduced production of beta chain, the patient has thalassemia major (when it is absent) or thalassemia intermedia when it is reduced. Thalassemia major is usually asymptomatic at birth because at this age, normally, the hemoglobin F is predominant. At 6 months of age, the patients present with severe anemia and hepatosplenomegaly. In patients with reduced production of beta chain, clinical spectrum will be beta thalassemia intermedia in which the patient will suffer less severe symptoms with the occasional requirement for blood transfusion and he enjoys long life survival.

4. Consequences

The two major consequences of thalassemia major are severe anemia, resulting from ineffective erythropoiesis, and iron overload resulting from regular blood transfusion and also increasing the rate of iron absorption in small intestine. Almost all complications of thalassemia major can be attributed to these two factors. Examples of these complications include skeletal changes, hepatosplenomegaly, growth retardation, multiple endocrine failure, and cardiac problem. Additionally, blood transfusion for anemia and chelation therapy for iron overload represent a major burden on the patient and his family and on the health resources where its prevalence is high. The only hope for children implicated with thalassemia major is bone marrow transplantation when it is done early in life before complications occur.

5. Hope for cure

Hematopoietic stem cell transplantation represents the only curative approach for those unlucky patients with thalassemia. Hematopoietic stem cells from a healthy donor replace the affected bone marrow and restore the normal hematopoiesis. The success rate is inversely correlated with the degree of iron overload and hepatic damage. The availability of healthy acceptable donor is another problem especially in societies with small family size as in China [8].

In areas where thalassemia rate is high, determination of carrier rate by population screening and prenatal diagnosis associated with genetic counseling is very useful by allowing couples at risk to decide about their reproductive choice after explaining the nature of the disease and the associated risk of having an affected child. It is clear that the only way to stop thalassemia is to prevent the birth of affected child by making the premarital screening tests for thalassemia carrier state compulsory for the general population and providing counseling for the affected families. Implementation of effective program for thalassemia control adopted by health authority with the help of international agencies like World Health Organization is fundamental for effective control of thalassemia in countries where its prevalence is high.

Author details

Isam Jaber Al-Zwaini

Address all correspondence to: ejkzwaini@yahoo.com

Department of Pediatrics, Al-Kindy Medical College, University of Baghdad, Iraq

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