Chapter 2

Thalassemias

The thalassemias are the most common of the hemoglobinopathies. The thalassemias are characterized by a quantitative defect in the globin synthesis of α or β globin chain. Decreased synthesis of one globin chain result in decreased hemoglobin synthesis and anemia. Furthermore, the imbalance of globin chains, with hemolysis and complications of ineffective erythropoiesis.

β-Thalassemias

Distribution and population at risk

β-Thalassemia is common in the populations of the Mediterranean region, the Middle East, India, Pakistan, Southeast Asia, Southern China and Indonesia. It is somewhat less common in Africa except for Liberia and certain regions North Africa. Estimates of gene frequencies are 3 - 10 % in some areas.[1]

The incidence of thalassemia in Thailand[2]

Thalassemia gene	%
α-thalassemia	20-30
Hb CS	1-8
β-thalassemia	3-9
Hb E	10-53

Thalassemia patients in Thailand[2]

Thalassemia	Number of patients
Homozygous β-thalassemia	2,070
Hb E/β thalassemia	96,390
Hb Bart's hydrops fetalis	833 (dead)
Hb H disease	336,000

Beta thalassemia

1. Thalassemia minor (thalassemia trait). The people in this group have small red blood cells and no or mild anemia.

2. Thalassemia intermedia (TI) or non-transfusion-dependent thalassemia (NTDT) is an inherited hemoglobinopathies characterized by a genetic and clinical heterogeneity.[2,3] The

patients with NTDT have significant anemia, but they are able to survive without transfusions. The diagnosis are:

- Many children with NTDT develop symptoms 2-6 years.
- Hemoglobin level range from 6 to10 g/dl or more, occasional transfusion.
- Hb H disease and some hemoglobin E/β-thalassemia patients.
- The degree of anemia tolerance.
- The threshold of the physician to transfuse thalassemia patients should be according to guideline.

The NTDT patient is more severe than thalassemia trait, but not require chronic blood transfusion. The NTDT patients may systematically require blood transfusions.[2-5]

3. Thalassemia major (TM) or transfusion-dependent thalassemia (TDT) is severe thalassemia in which chronic red cell transfusions are required. The condition begins between 6-24 months of age. The anemia is severe in some patients, that death occurs without blood transfusions. Some TDT could survive without blood transfusions, but would have deformities or complications. TDT are homozygous β-thalassemia and some hemoglobin E/β-thalassemia patients.[2,3]

Pathophysiology of thalassemia

Mechanisms of Anemia

Ineffective erythropoiesis, is a result of the detrimental effects of an alpha globin chains excess.[6]

Clinical Consequences of Anemia

The ineffective erythropoiesis effect in expansion of erythroid marrow to as much as thirty times the normal level. An increased plasma volume and splenomegaly may exacerbate severe anemia (Figure 2.1). Increased erythropoietin synthesis stimulate the extramedullary hematopoiesis such as the tissue in paraspinal region and the thorax. The expansion of marrow results in the face and skull deformities, osteopenia and bone mineralization disorder,[7,8] and may develop a periarticular syndrome by osteomalacia and micro-fractures.[9] Hyperplasia of marrow leads to more iron absorption and tissues iron deposition.

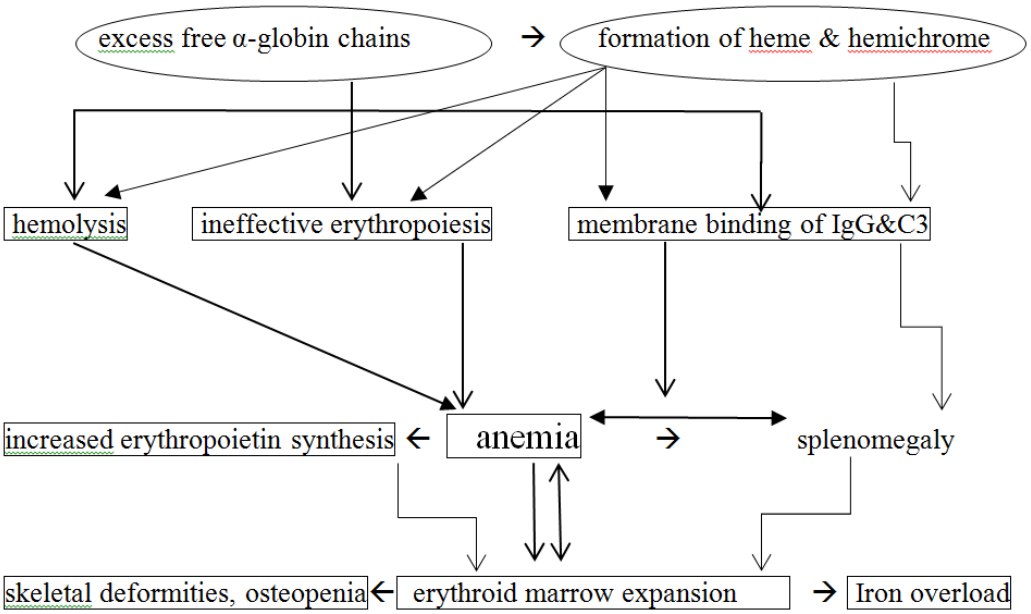

Figure 2.1 Effects of excess production of free α-globin chains. (adapted from Olivieri NF. 1999)

Alpha (α)-Thalassemias[1,2]

The α-thalassemia has been reported high prevalence in Africa, the Mediterranean region, the Southeast Asia and Middle East.

1. Carrier state. The patients have one gene deletion. They are hematologically normal.
2. Mild α-thalassemia. The patients have lost two genes of α-globin. They have mild anemia and small red blood cells.
3. Hemoglobin H disease. The patients have deletion of three α-globin genes. These patients have moderate to severe anemia and spleens enlargement. The clinical similar to β-TI in some patients. This disease caused by three genes (deletional Hb H) is less severe than cases in which two genes are deleted and has a point mutation of the third gene (non-deletional Hb H).
4. Hydrops fetalis. The patients have loss of all four genes of α-globin. The affected individual ordinarily suffer to the complications before birth and death.

Complication of thalassemias

Iron Overload

Tissue iron overload is fatal with or without blood transfusion if not prevented and or adequately treated. When the spleen breaks down red blood cells down, removing the globin and iron from these cells so that they can be reused. Iron overload is the most serious complication of β-thalassemia and it is a main focus of treatment.[10] In thalassemic patients who are untransfusions, abnormally regulated iron absorption results in increased in body iron burden ranging from 2 - 5 g/year, depending on the erythroid expansion severity.[11,12]

In the case inadequate of iron chelation, the deposition of iron in tissue results in dysfunction of cardiac, endocrine glands and liver.[10] The cardiac, changes correlated with chronic anemia are present in non-transfusion dependent patients and are aggravated by iron accumulation. In transfusion dependent thalassemic patients but are not receiving iron chelating agent, symptomatic heart complication was reported within ten years after the initiate of blood transfusions and may be precipitated by pulmonary arterial hypertension and myocarditis.[13,14] The survival of thalassemia is determined by the cardiac iron overload.[15,16]

Heart

The cardiac complications are the primary cause of death in TM patients and are the result of iron overload. The TI patients who do not usually have severe hemosiderosis are lower risk of heart complications.[15,16]

Metabolic problems

The hyperuricemia is a common manifestation in untreated TI patients because of the hypercatabolism of erythroid hyperplastic tissue and deficiency of folic acid.[17] Cholelithiasis, induced by the over production of bilirubin, is common in TI patient with an incidence of more than 50 %.[18]

Erythropoietic masses.

The chronic anemia of TI patients that are associated with hypoxia and defective hemoglobin unloading from fetal hemoglobin, increases the hemopoietic activity of bone marrow, leading

to extramedullary hematopoiesis. These masses can present in many sites, primary paravertebrale, the skull, the pleura and the pelvis.[17,19]

Leg ulcers.

The ulcers of leg over the medial malleolus are common site and troubled problem in TI patients. Their pathophysiology has been associated with chronic hypoxia caused by anemia,[19] abnormal circulation of the thalassemic red blood cells, high hemoglobin F concentration and venous stasis.

Endocrine glands

The endocrine abnormalities are more common in TM than TI in patients, according to the severity of iron overload and anemia. Hypogonadism is the most common endocrine problem, followed by diabetes mellitus and hypothyroidism.[20]

Osteoporosis and bone abnormalities.

The abnormalities of bone are present in TM and TI patients, as a result of the enhanced medullary hematopoiesis, bone deformities, osteopenia and pathologic fractures.[21] If started blood transfusion before the bone abnormalities have occurred, prevents bone complications.[21]

Pseudoxanthoma elasticum *(PXE)*

This defect consists primary of skin (larger coalescent plaques or small yellowish papules), ocular and vascular manifestations.[22]

Infections

The overwhelming postsplenectomy sepsis is a common and is a sudden event that can be rapidly mortal.[23]

Pulmonary arterial hypertension (PAH)

PAH complication, the leading cause of cardiac failure in TI patients. Almost 60 % of TI patients had PAH defined as Doppler peak systolic tricuspid gradient greater than 30 mmHg.[24]

Spleen and liver

Liver involvement is mainly due to extramedullary hematopoiesis, iron overload, virus, and hepatoma.[25,26] In the patients without blood transfusion, the splenic size increases with time, with consequent the anemia worsening.[25]

Hypercoagulability

Hypercoagulability is established in β-thalassemia with severe complications.[27-30] Its pathophysiology is primary characteristic to the genetic defect and its effect, iron overload and hemolysis. An oxidative stress is originated by these pathogenesis.[27]

Alloautoimmunization

The incidence of alloimmunization in thalassemia who received multiple blood transfusions has been reported 5 - 22 %.[31]

Control and Management

Prenatal diagnosis and prevention programs

Prenatal diagnosis, fetal blood sampling or chorionicvillus sampling for screening and disease prevention.[32]

Blood transfusions

Goals are achievement of optimal level of hemoglobin and avoid transfusion reactions.

Indications of transfusion in NTDT[2]

- Growth and development abnormalities
- Cardiovascular disease
- Extramedullary hematopoietic mass compression
- Bone deformities
- Chronic leg ulcer
- Thrombosis
- Splenomegaly and compression
- Recurrent infection
- Pregnancy

Medical therapy

- Iron-chelating therapy
- Folic acid. Folic acid deficiency caused by the increased hematopoiesis. Folic acid 1 mg per day supplementation is recommended for thalassemic patients.[32]

Bone Marrow transplantation

Indications of stem cell transplantation[2,32]

Patients develop severe anemia before the age of two years.

Patients with hemoglobin level less than 7 g/dl and TDT.

Conclusion

The thalassemias, relation between clinical multiplicity and the molecular pathophysiology of disease. These disease have become a principle part of clinical practice in the countries with large populations from the tropical areas. The noticeable increase in survival, to the fifth decade of life, of patients with well treated β-thalassemic patients in developed countries shows the most remarkable changes in mortality and morbidity related to a genetic disorder in this century. The thalassemias have emerged as a main problem of public health worldwide.

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