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Review Article

β-Thalassemia: A Current Overview

Abdul-Wahab M. Al-Saqladi

Department of Pediatrics, Faculty of Medicine and Health Sciences, University of Aden, Yemen.

Corresponding Author: Abdul-Wahab M. Al-Saqladi

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ABSTRACT

Beta-thalassemia is a group of hereditary blood disorders characterized by reduced or absent beta globin chain synthesis, resulting in chronic hemolytic anemia and ineffective erythropoiesis. Individuals with β-thalassemia have widely variable clinical manifestations, extending from nearly asymptomatic to severe anemia requiring lifelong regular blood transfusions and complicated by multiple organ damage. Chronic transfusion inevitably leads to iron overload which necessitates iron chelation therapy. Current overview about the disease clinical picture, method of diagnosis, complications and principles of management is going to be discussed in brief.

Key words: Thalassemia, anemia, hemoglobinopathies, blood transfusion, iron overload, iron chelation.

INTRODUCTION

Thalassemia is one of the most common hemoglobin disorders worldwide, with an estimated 365 thousands infants born each year with either thalassemia or sickle cell disease. [1] Thalassemia is a result of defective synthesis of α or β globin chains of hemoglobin (Hb A), and accordingly it is classified into α or β thalassemia. It is commonly inherited in an autosomal recessive mode.

The red blood cells in thalassemia carriers are less susceptible to invasion by Plasmodium falciparum, thus conferring a survival advantage for those individuals in malaria-endemic regions. The prevalence of thalassemia is highest in geographic regions were malaria infection was or still intensely transmitted, including the Mediterranean, sub-Saharan Africa, the Middle East, the Indian subcontinent, and Southeast Asia.

A mutation of the globin genes in beta- thalassemia leads either to reduce or complete absence of beta globin chains production. [2] This result in an imbalance between α- and β-globin chains and causes precipitation of the unpaired α-chains within red blood cell precursors or mature RBCs. This act as the primary trigger of pathophysiological changes, ultimately leads to ineffective erythropoiesis and chronic hemolytic anemia with associated consequences.

Clinical Features of β-thalassemia:

There are three clinical phenotypes, classified according to severity basically on blood transfusion requirements. These are β-thalassemia major, intermedia or minor. [3] In β-thalassemia major (also known as Cooley anemia), individuals usually present with anemia as early as the first year of life. The effects of hemolytic anemia and expansion of extramedullary hematopoiesis can lead to symptoms such as irritability, fatigue, jaundice, abdominal distention, hepatosplenomegaly, gallstones, poor growth and skeletal changes such as bossing of the skull, prominent maxilla and malar

eminences and depression of the nasal bridge. Patients are require regular blood transfusion (once every 3-4 weeks) and if not kept under good chelating therapy, iron accumulated and overload tissues in the heart, liver and endocrine glands result in cardiac myopathy, arrhythmias, liver cirrhosis and multiple endocrinopathies such as hypogonadism, bronze diabetes, hypopituitarism, hypothyroidism and hypoparathyroidism. The risk of transfusion related infection is increased especially hepatitis C.

β-thalassemia intermedia is characterizes by less severe anemia and require no or occasional transfusion, although serious complications can be developed such as skeletal changes, growth retardation, hypercoagulability and pulmonary hypertension.

β-thalassemia minor is asymptomatic with little or no anemia, microcytic changes in red cells may needs differentiation from iron deficiency anemia.

Diagnosis:

Microcytic hypochromic anemia is detected in CBC. Target cells and nucleated red blood cells in blood film. Hemoglobin electrophoresis or high-performance liquid chromatography (HPLC) can be diagnostic with predominant HbF, low or absent HbA, and elevated HbA2. Familial and DNA studies may be required to confirm the diagnosis and for genetic counseling. [4]

Complications:

Bone abnormalities: Skull changes are classic, with characteristic hemolytic facies contributed by failed pneumatization of maxillary sinuses and maxillary overgrowth with marked widening of the diploic space and "hair on end" appearance on skull radiography. Osteoporosis, osteopenia and pathological fractures may also occur. [5]

Iron overload: Iron overload resulted mainly from blood transfusions and, to a lesser degree, from increased iron gastrointestinal absorption. Regular transfusion could accumulate body iron by approximately 0.32-0.64 mg/kg/day. Free iron is a toxic substance and participates in the formation of reactive hydroxyl radicals, which cause denaturation of proteins and cellular damage. Therefore chelation therapy is the second most important treatment step after blood transfusion. Cardiac dysfunction and endocrinopathies are the most important complications of iron accumulation and must be assessed regularly during patient routine care. [6]

Growth delay and endocrinopathies: Physical growth and development are known to be impaired and attributed to chronic anemia and iron overload. Endocrinopathies such as hypothyroidism, delayed puberty, hypogonadism, growth hormone dysfunction are also contributory factors. Diabetes mellitus is seen after the age of 10 years and varied from impaired glucose tolerance to overt diabetes. [7]

Cardiac complications: heart failure and cardiac arrhythmias are the most common cause of death in thalassemia. The cardiac complications arise from iron overload, anemia, pulmonary disease, and myocarditis. [8]

Pulmonary hypertension: the increase pulmonary arterial pressure is detected by elevated regurgitant tricuspid jet velocity and has been observed in individuals with thalassemia intermedia undergone splenectomy. Restrictive lung diseases, disturbances in coagulation and nitric oxide dysfunction have been implicated in development of pulmonary hypertension. [9]

Splenomegaly and hypersplenism: spleen is invariably enlarged, but become more prominent in under-transfused individuals and it can exacerbate the anemia and occasionally cause neutropenia and thrombocytopenia as a result of hypersplenism. When this condition is occur or the transfusion requirement becomes unusually high splenectomy is indicated. [5] However, splenectomy is associated with increased risk of thrombotic complications and overwhelming infection.

Hypercoagulability: Beta-thalassemia major and intermedia are consider to be hypercoagulable states with tendency to thromboembolic events, this complication is exaggerated by the effect of splenectomy. Red cell membrane alterations act as strong procoagulant, in addition to the activation of endothelial cells, platelets, monocytes with reduction of natural anticoagulants such as protein C, S and antithrombin III. [10]

Infections: the rate of infection is increase in children particularly post-splenectomy for encapsulated organisms more importantly Pneumococci, H. influenzae, and Neisseria meningitides. Risk of blood born infections include viral (Hepatitis B and C, HIV), bacteria and parasite (e.g. malaria) is also increased. [11] Specific bacterial infection with Yersinia enterocolitica is related to iron overload and deferoxamine therapy.

Management:

Long-term management includes regular blood transfusion and treatment of iron overload as part of comprehensive management program. [12] In most patients with β-thalassemia major, transfusion is initiated before 2 year of age and the main aim is to maintain pre-transfusion hemoglobin at the level of 9 to 10 g/dL which require about 10-15 ml of leuko reduced packed red cell transfusion every 2-5 weeks. [13] After about 10 transfusions iron chelation must be consider with assessment of iron level in blood (serum ferritin), in the liver (liver iron content) and in the heart (MRI $T2^{*}$). Three iron chelatorsare available deferoxamine (injectable), deferiprone, and deferasirox (oral) can be used separately or in combination. [14] Patient adherence is important determinant of effective chelation therapy. If transfusion requirement exceeds 180-200ml/kg/year splenectomy should be considered. [15] Hematopoietic stem cell transplantation is currently the only available curative therapy, however it is an expensive option and not available for individuals living in low resource countries. The combination of gene therapy and HbF induction is a proposed therapeutic approach that can improve the disease pathophysiological features. [16]

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