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Review Article

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An Overview on Thalassemia Diagnosis and Management Approach, Literature Review

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ABSTRACT

Thalassemia syndromes are the most common inherited monogenic diseases that kill and affect millions of people worldwide. As Thalassemic diseases became a healthcare system burden for many countries around the world Thalassemia management emerges as a lifetime treatment program that should regularly be monitored with preferable choice for management. In this review we aim to collect and summarize recent articles, studies, and clinical trials in diagnosing and managing thalassemia, and provide a summarized, yet comperhansive study. PubMed database was used for this review and data was collected from relevant journal articles, randomized controlled trials, and observational studies containing the term used in the mesh "Thalassemia" "Management" "Diagnosis" "Laboratory" "Treatment" within the title or abstract. The major pathophysiological change that occurs in thalassemia is the imbalance of the globin chain production. Thalassemia management emerges as a lifetime treatment program that includes intensive medical and surgical care with ongoing monthly clinical visits.

Key words: *Thalassemia, Diagnosis, Clinical laboratory, Management, Treatment*

INTRODUCTION

In 2006, WHO declared thalassemia as a major health issue worldwide [1-3]. Thalassemia syndromes are the most common inherited monogenic diseases that kill and affect millions globally. It is globally estimated that 1-5% of the population worldwide are mostly carriers for thalassemia syndromic mutations [4, 5]. Moreover, various forms of thalassemia affect approximately about 56000 conceptions and 300000 babies annually [6]. Thalassemic diseases became a healthcare system burden for many countries around the world especially in Gulf Cooperation council countries where the prevalence of Alpha thalassemia carriers are lower than Beta thalassemia major carriers. Individuals with minor manifestations of the syndrome can be asymptomatic and usually, do not need treatment, while major manifestations that start at a young age are managed with intensive care and regular transfusion therapy [7].

This review will outline recent researches in managing thalassemia and will assist pediatricians and healthcare personnel in better understanding thalassemia and ultimately improving patient care.

MATERIALS AND METHODS

This comprehensive medical review is collected for the PubMed/MEDLINE only provided with these search terms: ((“Thalassemia "[Mesh] AND “Diagnosis” [Mesh] AND “Treatment” [Mesh] AND “Management” [Mesh])). Only published articles, trials, and documents were recorded in this review. Publications describing thalassemia epidemiology, clinical assessment, and/or management were all included.

Review

Epidemiology

Thalassemia has become a major concern in many countries and their health systems around the world since 2006 according to the WHO [1]. About 56000 conceptions end up as thalassemic patients. Furthermore, about a 1.33million pregnancies for thalassemia carriers are at high risk for the major thalassemia syndrome. About 300,000 babies born worldwide are affected with thalassemia annually. Thalassemic diseases became a healthcare system burden for many countries around the world especially in Gulf Cooperation council countries where the prevalence of Alpha thalassemia carriers are lower than Beta thalassemia major carriers [7]. Moreover, in many other developing countries thalassemia became the main cause of death because of the expensive management and the noticeable absence of the proper measures in managing hemoglobinopathies [8, 9].

Diagnosis and subtypes of thalassemia

Genetic hemoglobinopathies are caused by mutations that occur in globin genes. The major pathophysiological change that occurs in thalassemia is the imbalance of the globin chain production. Different structural malformations occur on both involved alpha or beta globin chain that alters fetal hemoglobin leading to severe forms hemolytic anemia [10].

Alpha thalassemia is a heterogeneous molecular defect that is associated with numerous alpha-globin gene deficits that alter the alpha goblin chain. Alpha thalassemia 1 is one of the most severe forms as it involves mutation and duplication of the alpha-globin gene. However, milder forms of mutations that are rare include two subtypes of alpha thalassemia, deletional and non-deletional alpha thalassemia [11].

Beta thalassemia has different molecular defects as most of the mutations in the beta-globin have based substitutions of one or two nucleotides. In severe forms of homozygous Beta-thalassemia children may appear healthy at birth because of the functioning Hb F. However, after 8 to 12 months of life, it may become asymptomatic but highly pathogenic with no beta globin expressions. Mutations and malformations of the globin genes form impaired chains that reduce the hemoglobin content causing mild to severe microcytic anemia [11].

Diagnosing and detecting thalassemia and other hemoglobinopathies begin with relevant family history, laboratory screening, and invasive prenatal screening via obtaining amniocentesis and chorionic villus sampling when the parents are at high risk for hemoglobinopathies. Moreover, new molecular genetic technologies to map and detect mutation and deletion by sequencing analysis prenatally [10, 12, 13]. Most of these technologies include PCR screening for mutations, electrophoresis, high-performance liquid chromatography (HPLC), and DNA test [10, 14].

Clinically, thalassemia classification depends on the variant type (deletion and non-deletion variants) and the location of the globin within the genes. These variants are examined by several applicable diagnostic molecular techniques in the clinical laboratory that has a direct impact on the accuracy of the diagnosis of thalassemia [15]. **Table 1** describes a brief idea about the common use of molecular techniques for detecting minor genetic mutation, deletion, and insertions [10].

Table 1. Molecular techniques used to detect minor genetic mutation, deletion, and insertions [10].

Techniques for known mutations	Techniques for unknown mutations
- Allele-specific PCR - Gel electrophoresis - Real-time PCR with melting curve analysis - Dot blot analysis	- Denaturing electrophoresis gradient gel - Mismatched analysis - Direct DNA sequencing

Multisystem evaluations should be done frequently to ensure any systemic involvement of the disease or progression. Based on any clinical suspicion, imaging is necessary to be done as in gallbladder and biliary tract imaging, cardiac MRI, abdominal ultrasonography to assess and determine the carrier systemic status [16].

Challenges of management in thalassemia

The care and assessment for thalassemia patients seem pretty challenging as it varies widely depending on the type, subtype, and severity of the underlying syndrome. There are have been effective and adequate treatment programs that are applied parallel with awareness are possible for prevention from thalassemia. Usually, alpha thalassemia carriers do not need treatment. However, carriers of alpha thalassemia can suffer nutritional deficiencies related to homogenesis such as iron deficiency anemia or vitamin B 12 deficiency [17]. On the other hand, the beta-thalassemia carrier's basic clinical manifestation is chronic anemia. However, beta-thalassemia carriers are treated based on their clinical situation: major, intermedia, and minor [18].

The lifetime treatment of thalassemia includes intensive iron chelation medications and blood transfusion, hematopoietic stem-cell transplant, routine laboratory investigations, and recurrent clinical visits for follow-up. However, the challenges and limitations that might interfere with the process of management can obstruct any wanted results. Thalassemia major carriers are usually treated with blood transfusion to treat symptoms of severe anemia and developmental delays [19].

In cases of chronic anemia, iron status should regularly be monitored as it reflects the balance and imbalance of iron and evaluates any signs of iron overload. Iron overload and raised serum ferritin levels are serious problems in thalassemia as well as in other hereditary hemolytic anemias. Iron overload toxicity is associated with increased morbidity rates in both patients with non-transfusion-dependent thalassemia (NTDT) and transfusion-dependent thalassemia (TDT) and several vital organs are affected differently by the underlying condition. Classically, the most prominent and complex clinical complication and has been a major cause of mortality in iron overload is cardiac siderosis. Other endocrine and hepatic dysfunctions are also observed in transfusion-dependent thalassemia [18, 20]. **Table 2** discuss the iron overload complications in both NTDT and TDT [20].

Table 2. Iron overload complications in Transfusion dependent thalassemia and Non-dependent transfusion thalassemia [20]

Systems	Transfusion dependent thalassemia	Non- transfusion dependent thalassemia
Cardiovascular	Siderosis left ventricular failure	Pulmonary hypertension, venous thrombosis, right ventricular heart failure
Liver	Liver fibrosis, Viral hepatitis, and cirrhosis	Liver fibrosis, hepatocellular carcinoma, liver cirrhosis
Endocrine	Hypothyroidism Developmental retardation Hypoparathyroidism Osteoporosis Hypogonadism Diabetes mellitus	Osteoporosis
Other		Gallstones Leg ulcers Hematopoietic extramedullary tumors, silent cerebral ischemia

Iron chelation therapy is required in iron overload management after confirming several noninvasive confirmation assessments that involve serum ferritin levels monitoring [20]. The aim of adding iron chelators includes maintaining a safe iron load and removes deposited excess iron loads in the tissues that promote reversal organ failure effects. Three iron chelators are actively used. The first effective oral film-coated Deferasirox tablet is an advanced oral chelator that is well tolerated and is given at 20-30mg/kg once/day [21]. Deferipone tablets also have proven efficacy in removing iron overload from several vital organs mainly the heart [22]. However, Deferoxamine is subcutaneously infused slowly and continuously through a portable pump [23].

Stem cell transplant remains be a preferable choice in some selected cases as it can diminish the probability of the need for blood transfusions [24]. Although stem cell transplant is considered a potential option this

procedure has its challenging risks that include graft failures, immunosuppressive therapy, graft vs host disease, and transplantation-related mortality [25].

Patients with thalassemia can undergo splenectomy and cholecystectomy in many phases as part of the therapeutic process. Splenectomy limits the number of blood transfusions and regresses the spread of extramedullary hematopoiesis [26]. Cholelithiasis can occur in thalassemia after Hemoglobin breakdown and the influence of bilirubin deposition in the gallbladder if it becomes symptomatic patients should undergo cholecystectomy with splenectomy [27].

Follow-up thalassemic patients are asked to monitor the progress of the disease as its recommended to have a clinical visit every month for routine physical and clinical laboratory assessments. Also, a Multisystemic assessment is recommended to be performed every two months up to every 6 months. In Gilbert syndrome patients, it's recommended to perform gallbladder echography to detect cholelithiasis [28, 29].

CONCLUSION

Thalassemia has been declared a major health issue worldwide. The major pathophysiological change that occurs in thalassemia is the imbalance of the globin chain production. Thalassemia management emerges as a lifetime treatment program that includes intensive medical and surgical care with ongoing monthly clinical visits. However, health professions should carefully review clinical laboratory results especially in cases of chronic anemia where the iron status should regularly be monitored and undergo focused physical examinations for other multisystemic complications and associated thalassemia complications that are suspected.

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