The Egyptian Journal of Hospital Medicine (Apr. 2017) Vol. 67(1), Page 407- 414

A Review of β-Thalassemia in Saudi Arabian Children

Jassim Mohammed Ali Aljaryan
Pediatric Department, Maternal and Child Hospital, Dammam

ABSTRACT

Beta-Thalassemia being particularly prevalent in the Mediterranean region. Thalassemia syndromes are common in Saudi Arabia: the Beta-Thalassemia genes occur with variable frequency in different regions of Saudi Arabia and both B+ and Bo thalassemia have been reported. Over the last few years, a great deal of information regarding the clinical, molecular and management of these disorders has accumulated in the literature. This paper summarizes some of the recent studies on the subject along with experience and attempt to clarify the importance of early detection and treatment β- Thalassemia in children.

Keywords: Thalassemia, Saudi Arabian children, blood disorders.

INTRODUCTION

Thalassemia is an inherited blood disorder, which is characterized by decreased synthesis or absence of globin. This synthetic defect leads to the formation of fragile abnormal red blood cells (RBC), which can be easily hemolyzed, leading to chronic anemia[1]. This disorder is highly prevalent among children in the Middle East, Mediterranean region, and South Asia. However, only a few studies on pediatric quality of life (PedsQL) have been published from those areas[2]. The management of thalassemia includes regular blood transfusion, iron chelation therapy, and appropriate management of comorbidities. These modalities led to an increase in the life expectancy of thalassemic children. Thus, emphasizing the importance of maintaining the quality of life in children with thalassemia[3]. Thalassemia has a negative impact on the physical functioning of children and adolescents. It can also affect social relationships and mental health, eventually leading to poor school performance and overall impairment in the health-related quality of life (PedsQL). It has been reported that approximately 80% of thalassemic patients have psychiatric problems. It was reported previously that emotional distress and disease burden have an effect on the quality of life of patients in the form of depression and anxiety-related symptoms; however, culture and the type of treatment did not[4]. Pediatric quality of life measurement is a tool that is used to assess the effect of disease on a patient's well-being. Different aspects are covered in pediatric quality of life , including physical, psychological, and social functioning as various factors can affect quality of life.

Common definitions used in Thalassemia:

Beta thalassemia disorders result from decreased production of beta globin chains, resulting in the relative excess of alpha globin chains. The degree of excess nonfunctional alpha chains is the major predictor of disease severity. Beta0 thalassemia refers to the absence of production of beta globin.[5] When patients are homozygous for a beta0 thalassemia gene, they cannot make any normal beta chains (hemoglobin A). Beta+ thalassemia indicates a mutation that presents decreased but not absent production of beta globin. Thalassemia patients in whom one or both of their beta thalassemia mutations are beta+ mutations make some hemoglobin A, and the disorder may be less severe. Beta-thalassemia major is a clinical diagnosis referring to a patient who has a severe form of the disease and requires chronic transfusions early in life. Beta thalassemia intermedia are a clinical diagnosis of a patient characterized by a less severe chronic anemia and a more variable clinical phenotype. Alpha thalassemia refers to a group of disorders characterized by inactivation of alpha globin genes. This results in a relative increase in nonfunctional beta globin or gamma globin tetramers and subsequent cell damage. Normally, there are four alpha genes. Absence or non-function

Received: 20 / 02 /2017
Accepted: 25/ 02 /2017
DOI : 10.12816/0036655

of three alpha genes results in hemoglobin H disease, and the loss of all four alpha genes usually results in intrauterine death. This review is an attempt to highlight, in a simple way, the basic essentials of thalassemia and its variants.

Complications

The life of patients with thalassemia has improved both in duration and in quality in industrialized countries. Complications are still common and include heart disease (heart failure and arrhythmias), chronic liver hepatitis, which can evolve in cirrhosis and, rarely, in hepatocellular carcinoma, endocrine problems (hypogonadism, hypothyroidism, diabetes, hypoparathyroidism), stunted growth, osteoporosis, thrombophilia and pseudoxanthoma elasticum. The incidence of complications is decreasing in younger cohorts of patients who have been transfused with blood that has been screened for viruses and thanks to the introduction of new oral iron chelators and imaging methods. The accurate measurement of iron deposits allows better management of iron overload. In addition, therapy for several complications is available. Specialized competence in treating patients with thalassemia is of great importance[6].

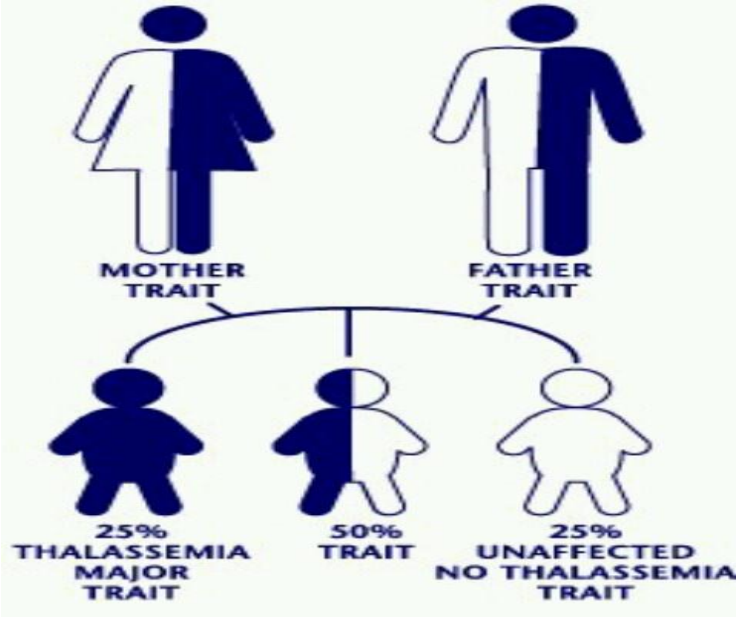

Figure 1: Thalassemia is an inherited blood disorder in which the body makes an abnormal form of hemoglobin[7].

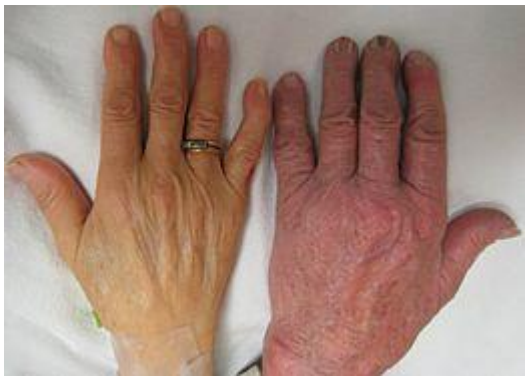

Figure 2: The hand of a person with severe anemia (left) compared to one without (right)

Causes

Thalassemias are inherited disorders caused by various gene mutations. The clinical expression and severity are subject to numerous factors that may either mask the condition or exaggerate the symptoms, leading to a more severe disease[8].

Signs and symptoms

The clinical picture of the thalassemias varies widely, depending on the severity of the condition and the age at diagnosis. In the more severe forms of the disease (eg, β-thalassemia major), symptoms vary from extremely debilitating in patients who are not receiving transfusions to mild and almost asymptomatic in those receiving regular transfusion regimens and closely monitored chelation therapy.

Signs and symptoms of different types of thalassemia include the following:

- More severe forms: some pallor, slight scleral icterus, enlarged abdomen
- Rare types of β-thalassemia trait: severe hemolytic process requiring management, such as thalassemia intermedia or thalassemia major
- Hb E/β thalassemia: may have severe symptoms and clinical course identical to that of β-thalassemia major
- Heterozygous/homozygous Hb E: usually slightly anemic and usually asymptomatic
- A-Thalassemia: clearly evident hematologic abnormalities in newborns with mild or moderate forms of the disease
- B-Thalassemia: extreme pallor, swollen abdomen due to hepatosplenomegaly
- Severe bony changes due to ineffective erythroid production (eg, frontal bossing, prominent facial bones, dental malocclusion)
- Hypermetabolism from ineffective erythropoiesis
- Gout due to hyperuricemia (occasionally)
- Iron overload: one of the major causes of morbidity in all patients with severe forms of thalassemia
- Growth retardation, failure to thrive
- Metabolic symptoms that suggest diabetes, thyroid disorder, or other endocrinopathy
- Neuropathy/paralysis in patients with severe anemia not receiving transfusion therapy

DNA Testing

Prior to treatment because of the enormous diversity in clinical severity of thalassemia patients, complete DNA testing prior to the commencement of treatment is required to determine prognosis, appropriate therapy, and family counseling. Definitive diagnosis and family counseling should be done in conjunction with a thalassemia center.

Diagnosis of Thalassemia

Prior to consideration of transfusion therapy, it is critical to confirm the patient's diagnosis. In addition, to complete blood count (CBC), hemoglobin electrophoresis is the first diagnostic test. Fractions of hemoglobin A, A2, F, H, E, and other variants are measured. Hemoglobin analysis by hemoglobin electrophoresis or high-performance liquid chromatography is used. Mutations may overlap on the screening test, resulting in incorrect diagnosis or a false negative. Therefore, genetic analysis for both beta-thalassemia and alpha-thalassemia mutations are necessary. In addition, parents and siblings should be screened. Occasionally (up to 20 percent of the time), only a single mutation will be found that is indicative of thalassemia trait. Some of these cases result from an autosomal dominant form of thalassemia and others from inheriting a mutation that is not detected by the probes utilized in the DNA testing. Alpha-gene triplication is a common co-factor that may convert a thalassemia trait to a disease or worsen a benign mutation. Testing for co-mutations needs to be requested from the DNA laboratory otherwise, it will not be performed. Patients with thalassemia intermedia may have exaggerated anemia due to temporary nutritional deficiencies or infectious complications. It is important to complete a detailed medical history concerning factors that may temporarily lower hemoglobin, including viral illness, marrow-suppressing medication, or exposure to environmental factors such as lead. Nutritional deficiencies in folic acid or iron may exaggerate anemia. Correcting these deficiencies may raise the hemoglobin level enough to obviate the need

for transfusion. Therefore, laboratory screening of patients is necessary to rule out other causes of anemia. Measurements should be taken of the G6PD level, serum ferritin, total iron-binding capacity, serum iron, and red cell folate. A brief therapeutic trial of iron (6 mg/kg/day for four to eight weeks) and folic acid (1 mg/day) are indicated if significant laboratory deficiencies are found[9].

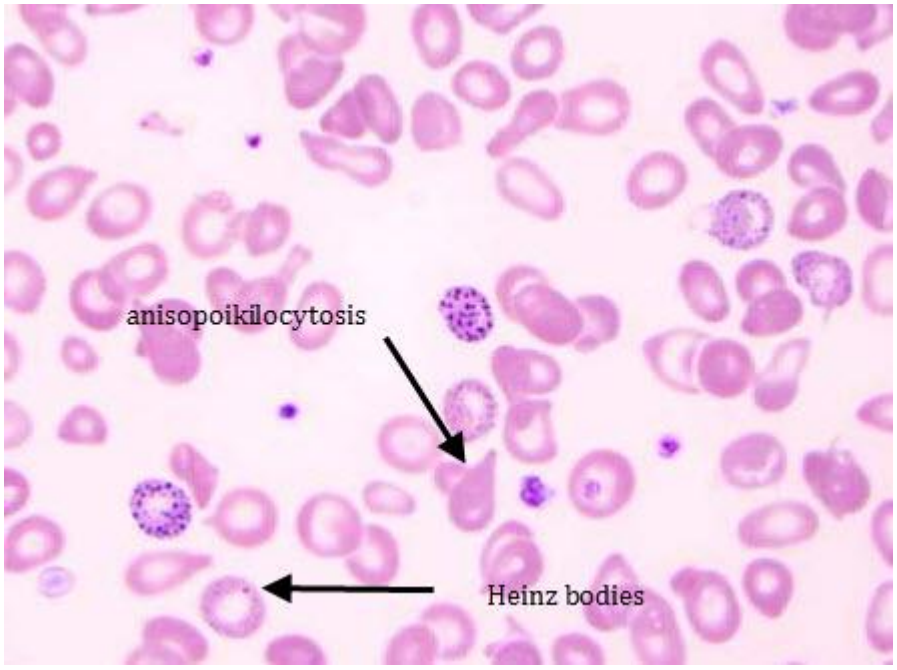

Figure 3: blood film shows B thalassemia

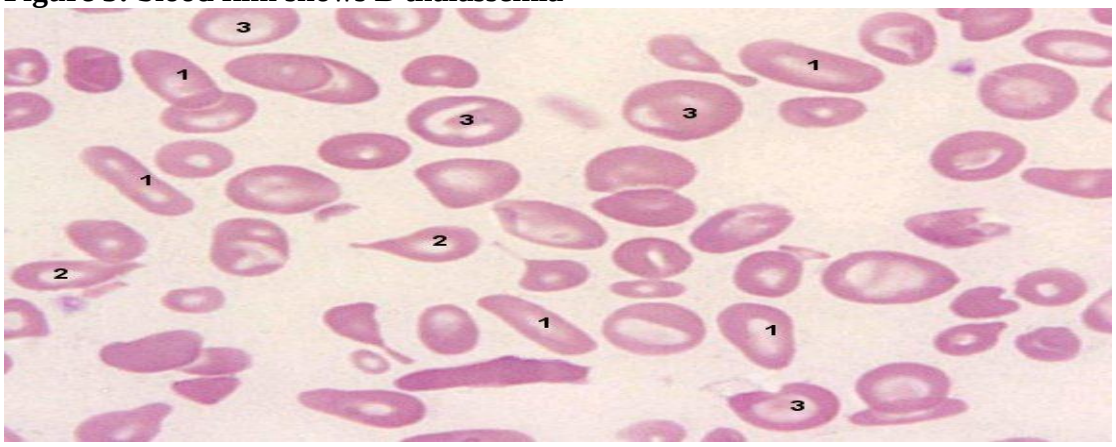

Figure 4: Blood film shows B thalassemia

Management

Patients with thalassemia traits do not require medical or follow-up care after the initial diagnosis is made. They also do not initiate iron therapy unless a definite deficiency is confirmed.

Patients with severe thalassemia require medical treatment. Regular blood transfusion combined with well-monitored chelation therapy is the standard therapy[10].

Pharmacotherapy

- Antipyretics, analgesics (eg, acetaminophen)
- Antihistamines (eg, diphenhydramine)
- Chelating agents (eg, deferoxamine, deferasirox)
- Corticosteroids (eg, hydrocortisone)
- Antibacterial combinations (eg, TMP/SMX, gentamicin, penicillin V)
- Vitamins (eg, ascorbic acid, alpha-tocopherol, folic acid)
- Vaccines (eg, polyvalent pneumococcal; 7-valent pneumococcal conjugated; *H influenzae* type B; meningitis group A, C, Y, and W-135)
- Antineoplastics (eg, hydroxyurea)
- Growth hormone (eg, somatropin)

The FDA has expanded the approved use of deferasirox to treat children aged 10 years and older with chronic iron overload due to nontransfusion-dependent thalassemia (NTDT). The agency recommends administration of deferasirox in such children who have a hepatic iron concentration of at least 5 mg of iron per gram of dry liver weight. Previously, deferasirox was approved for managing chronic iron overload due to blood transfusions in patients ages 2 years and older[11].

Surgical options

- Splenectomy: principal surgical procedure for many patients with thalassemia
- Placement of central line: for the ease and convenience of administering blood transfusions, chelation therapy, or both in patients with severe thalassemia on transfusion therapy.

Pain Syndrome in Thalassemia

Chronic pain has not been noted as a major component of the symptoms of thalassemia. However, in the last decade, as prognosis has improved, cumulative tissue injury appears to be resulting in chronic pain syndrome. A recent study utilizing the Brief Pain Inventory (BPI) assessed pain in 250 thalassemia patients in North America. Two-thirds of the patients reported repeated pain episodes each month, and 20 percent reported daily pain. The prevalence and severity of pain correlated with age of the patient. As patients age, pain becomes a more prominent problem in their lives. Most patients have back pain. Three-quarters of the patients were taking non-steroidal analgesics for pain relief. In addition, 24 percent were receiving short-acting narcotic analgesics, and another 11 percent were receiving long-acting narcotic analgesics. Pain assessment on a regular basis is recommended for all patients.[12] While transfusion therapy may decrease the pain in thalassemia intermedia, this has not been prospectively evaluated. All patients should undergo assessment for causes of pain, including extramedullary masses, osteoporosis, and spinal fractures, as well as other less common problems, such as secondary gout and thrombosis[13].

Acute Infection

Acute infection remains a major cause of death in thalassemia patients. A vigilant approach to recognize and treat serious infections will prevent unnecessary mortality. Patients should be educated on management of fever and acute symptoms, with advanced understanding of who to call and where to seek care. Easy access to medical records can assist in the rapid assessment and treatment of patients. This can be facilitated by patients carrying health records listing diagnosis, complications, and treatments. Prophylactic antibiotics for splenectomized patients do lower the risk of pneumococcal infections. However, gram-negative organisms are the major cause of bacteria in thalassemia patients. Prompt treatment with broad spectrum antibiotics should start before the results of blood cultures are indicated. Patients with central venous catheters may have staphylococcus epidermidis and require vancomycin therapy. Thalassemia patients have an increased risk of Yersinia enterocolitica. This iron-avid organism may present clinically with fever, abdominal pain, and diarrhea. Antibiotics should be started before stool and blood culture results are available. In general, all chelation therapy should be stopped until the febrile illness is adequately treated[14].

Nutrition

Nutritional deficiencies are common in thalassemia, due to hemolytic anemia, increased nutritional requirements, and morbidities such as iron overload, diabetes, and chelator use. Patients should be evaluated annually by a registered dietitian regarding adequate dietary intake of calcium, vitamin D, folate, trace minerals (copper, zinc, and selenium) and antioxidant vitamins (E and C). Annual nutritional laboratory testing should include albumin, 25-hydroxy vitamin D, fasting glucose, fasting plasma zinc, serum copper, ceruloplasmin, serum selenium, alpha and gamma tocopherol, plasma ascorbate, and serum folate. (See nutrition table below.)

Recommendations for dietary supplementation should be made as indicated by nutritional history, complications of the disease, and, in children, growth status. Typically multivitamin supplementation without iron is suggested (e.g., Centrum Silver in tablet or chewable form is now available). For nontransfused thalassemia patients, folate supplementation (1 mg daily) is recommended, and consuming a moderately low iron diet is encouraged—that is, avoiding iron-fortified cereals and other products and excessive consumption of red meat. Drinking black tea with meals is recommended to reduce iron absorption from food. For transfused patients on chelation therapy, a low-iron diet is unnecessary and may decrease the quality of life for some patients. The amount of iron obtained from just one unit of packed red cells (200 mg) far outweighs the amount of iron obtained from a 3-ounce steak (5 mg). Vitamin D supplementation (50,000 IU once a week until levels normalize) is recommended for patients with a 25-hydroxy vitamin D less than 20 ng/dL. Calcium supplementation should be encouraged if dietary intake is insufficient. Counseling should be offered for patients with special dietary needs. These include patients with diabetes or lactose intolerance, those who practice vegetarianism, those who are pregnant, or those on oral chelators or bisphosphonate medications. Alcohol consumption and cigarette smoking are to be discouraged. Alcohol potentiates the oxidative damage of iron and aggravates the effect of hepatitis B and C on liver tissue. Cigarette smoking affects bone remodeling and is associated with osteoporosis[15].

Nutrition Table Recommended for Patients

Nutrient	**Diagnosis of adequacy**	**U.S. dietary recommended intake**	**Tolerable upper limit**
Calcium	Serum calcium not informative as it is buffered.	19 to 50 years—1,000 mg/day 9 to 18 years—1,300 mg/day 4 to 8 years—800 mg/day	2,500 mg/day
Vitamin D	Serum 25-hydroxy vitamin D > 30 ng/mL	400 IU per day	10,000 IU/day for adults; unknown for children
Folate	Serum or plasma folate > 3 ng/mL	1 mg per day for nontransfused patients	Unknown for thalassemia patients; for general population, suggested upper limit is 1 mg/day
Zinc	Fasting morning plasma zinc > 70 µg/dL	Women/girls: 8 mg/day men/boys: 11 mg/day 4 to 8 years: 5 mg/da	Over 19 years—40 mg/day 14 to 18 years—34 mg/day 9 to 13 years—23 mg/day
Copper	Serum copper > 70 µg/dL	19 to 50 years—900 µg/day 14 to 18 years—890 µg/day 9 to 13 years—700 µg/day 4 to 8 years—440 µg/day	Over 19 years—10 mg/day 14 to 18 years—8 mg/day 9 to 13 years—5 mg/day
Ceruloplasmin	Ceruloplasmin > 17 mg/dL	N/A	N/A
Selenium	Serum selenium > 45 µg/L	19 to 50 years—55 µg/day 9 to 18 years—40 µg/day 4 to 8 years—30 µg/day	400 µg/day
Vitamin C	Plasma or serum ascorbate > 0.4 mg/dL (avoid hemolysis)	75 to 90 mg/day If on chelation, 100 to 250 mg/day recommended	Unknown for thalassemia patients; for general population, suggested upper limit is 2,000 mg/day
Vitamin E	Serum or plasma fasting alpha and gamma tocopherol (see local lab for normal for age and gender)	Adults: 100 IU/day	Unknown for thalassemia patients; for general population, suggested upper limit is 1,000 mg/day

Notes: All trace elements (zinc, copper, selenium) need to be collected into trace element–free vacutainers. Normative values may be somewhat different depending upon the reference lab. The upper limit for vitamin D is 10,000 IU when taken daily; much higher doses (e.g., 200,000 IU) have been used in vitamin D–deficient patients when taken weekly or monthly. 1 mg vitamin E = 0.45 to 0.67 IU vitamin D, depending upon the form of vitamin E.

Child life services

Culturally sensitive child life services are an integral part of comprehensive care. Child life services assure that care is family centered and developmentally appropriate for the patient. It is imperative that patients with thalassemia understand their disease and treatment in order to follow their prescribed medical regiments. Child life programs in health-care settings minimize psychological trauma and promote optimal development of children and their families. Through observation and discussion, assess the response of the patient and family to health-care experiences, and develop a plan to meet their needs and facilitate coping. Provide opportunities for gaining a sense of mastery, for play, for learning, for self-expression, for family involvement, and for peer interaction. This can be achieved in many ways, including medical play and art therapy. Provide a positive growth experience for patients. Minimize stress and anxiety for the patient, parents, and siblings. Giving continual teaching to patients to help them understand all aspects of thalassemia, including blood type and transfusion, chelation, and general health and wellness. Prepare children and families for health-care experiences. For example, conduct a medical preparation prior to a patient's liver biopsy/SQUID and splenectomy. This increases overall understanding of the procedure, reduces anxiety, and enables patients to gain mastery over their health-care experiences. During hospitalizations, provide essential life experiences such as play, school, peer interaction, community events. These activities commonly take place in the hospital playroom or schoolroom. Also, create opportunities that strengthen self-esteem and independence. Child life specialists are an integral part of the health-care team. They can work to empower patients and families, as well as teach them to be proactive members in their own health care. Child life can also assist with transitional issues as patients get older and new issues and challenges arise.

The b-thalassemias are also common in Saudi Arabia along the coastal strip of the Red Sea and in the Eastern province around Jubail, Qateef, Dammam, and Hofuf. Although the b-thalassemia disease has been known for many years in these areas and many of its manifestations are recognized, the details of actual incidence, the natural history or clinical course of the disease from early childhood to death are unknown. This is largely because of inadequate facilities for mass population screening, variable severity, and manifestations, and complexity of the interaction of the disease process with other health related events eg. sickle cell disease. There are at least 150 transfusion-dependent homozygous b-thalassemia patients who are receiving medical care at local hospitals in the Eastern Provincer. Despite the prevalence of thalassemias and other blood genetic disorders in Saudi Arabia, there is little common knowledge in the profession.

Medications

Multiple blood transfusions can result in iron overload. The iron overload related to thalassemia may be treated by chelation therapy with the medications deferoxamine, deferiprone, or deferasirox. These treatments have resulted in improving life expectancy in those with thalassemia major[16].

Deferoxamine is only effective via daily injections which make its long-term use more difficult. It has the benefit of being inexpensive and decent long-term safety. Adverse effects are primary skin reactions around the injection site and hearing loss.

Deferasirox has the benefit of being an oral medication. Common side effects include: nausea, vomiting and diarrhea. It however is not effective in everyone and is probably not suitable in those with significant cardiac issues related to iron overload. The cost is also significant.[16]

Deferiprone is a medication that is given by mouth. Nausea, vomiting, and diarrhea are relatively common with its use[16]. It is available in both Europe and the United States[17]. It appears to be the most effective agent when the heart is significantly involved.

There is no evidence from randomized controlled trial to support zinc supplementation in thalassemia[18].

CONCLUSION

Thalassemia syndromes are common in Saudi Arabia. The β thalassemia genes occur with variable frequency in the different region of Saudi Arabia. The importance of the better understanding of the pathophysiology, clinical manifestation and management is stressed. In the case of thalassemia in Saudi Arabia, however, it still has a long way to go, in establishing the frequency, characteristics and population densities of the disease. An important aspect of the problem that population lacks genetic counseling service within the current state of health services must hold priority.

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