Hemoglobin, 2013; Early Online: 1–11

ISSN: 0363-0269 print/1532-432X online
DOI: 10.3109/03630269.2013.825841

informa healthcare

ORIGINAL ARTICLE

β- AND α-THALASSEMIA INTERMEDIA IN BASRA, SOUTHERN IRAQ

Dhurgham A. Abdulwahid,[1] and Mea'ad K. Hassan[2]
[1]*Department of Pediatrics, Basra Maternity and Children Hospital, Barsa, Iraq*
[2]*Department of Pediatrics, College of Medicine, University of Basra, Basra, Iraq*

□ *Hemoglobinopathies are common in Iraq and β-thalassemia major (β-TM) is a leading health problem in Basra, Southern Iraq. However, β- and α-thalassemia intermedia (β- and α-TI) have not been so well studied. This is a descriptive study of 152 consecutive β- and α-TI patients registered at the Centre for Hereditary Blood Diseases (CHBD) in Basra, Southern Iraq from October 1 2010 through June 30 2012 including age at diagnosis, blood transfusions and complications. β-Thalassemia intermedia was found in 80 (52.6%) patients with a mean age at diagnosis of 7.10 ± 8.0 years. This was significantly different from that of Hb H (β4) disease (12.95 ± 14.8 years),* $p < 0.05$*. Patients with β-TI received significantly more blood transfusions (3.39 ± 3.85)/year compared to those with Hb H disease (1.07 ± 1.39)/year,* $p < 0.05$*.*

Short stature, extramedullary erythropoiesis, pulmonary hypertension and iron overload were significantly higher among patients with β-TI compared to those with Hb H disease, $p < 0.05$*. Iron overload is a significant risk factor for growth retardation among patients with Hb H and β-TI. While age is a significant risk factor for osteoporosis in both types of thalassemia intermedia.*

Both α- and β-thalassemia (α- and β-thal) have been reported in Basra. Although β-TI is associated with a more severe disease than α-TI, both are associated with considerable complications. Thus, genetic studies are needed to determine the types of mutation producing β-TI and the exact α-thal determinants producing Hb H disease as they are important in the prediction of the phenotype severity.

Keywords β-Thalassemia intermedia (β-TI), α-Thalassemia intermedia (α-TI), Hb H (β4), Basra, Southern Iraq

Received 26 October 2012; Accepted 23 April 2013.
Address correspondence to Professor Mea'ad K. Hassan Department of Pediatrics, College of Medicine, University of Basra, Al-Bradheya, Basra, Iraq; Tel.: +9647801000174; Fax: +964780640157; E-mail: alasfoor_mk@yahoo.com

INTRODUCTION

As a group, thalassemia represents the most common single genetic disorder known, and in many parts of the world, these diseases constitute a major public health problem (1). These disorders are more prevalent in the Eastern Mediterranean where 4.4% of the population are carriers of clinically significant variants including Hb S [β6(A3)Glu→Val; *HBB*: c.20A>T], Hb C [β6(A3) Glu→Lys; *HBB*: c.19G>A], Hb E [β26(B8)Glu→Lys; *HBB*: c.79G>A], β-thalassemia (β-thal) and α^0-thalassemia (α^0-thal). Around 0.7/1000 of conceptions are affected with thalassemia including homozygous β-thal, homozygous α^0-thal and Hb H (β4) disease (2).

The carrier rate for the β-thal gene in Iraq ranges from 3.7–4.6% (3–5); however, there are no published data about the carrier rate of α-thal in Iraq. According to WHO (World Health Organization), the annual birth rate for β-thal is estimated to be around 10,000 in the Eastern Mediterranean region; 90.0% of whom become transfusion-dependent and there are more than 7000 deaths annually when appropriate care is not available (2).

Basra is located in the extreme south of Iraq, sharing borders with Kuwait, Iran and Saudi Arabia, and has an estimated population of 2,531,997. A previous study in Basra reported a carrier rate of 4.6% for β-thal genes and an annual birth rate of 0.52/1000 for homozygous β-thal (5). Very little epidemiologic data are available about the less severe phenotypes with a good number of patients with β-thal intermedia (β-TI) born annually in Basra or other parts of Iraq.

Thalassemia intermedia is a clinical syndrome that includes patients having thalassemia of moderate severity [hemoglobin (Hb) 7.0–10.0 g/dL] who do not need regular transfusions. This clinical syndrome may be caused by a variety of genetic defects including β-TI and α-thal intermedia (α-TI) (6). At one end of the spectrum are individuals who, except for mild anemia, are symptom free. At the other end, there are patients who have Hb values in the range of 5.0–7.0 g/dL, marked splenomegaly, severe skeletal deformities, and as they get older, become heavily iron loaded because of increased intestinal absorption of iron. Recurrent leg ulceration, folate deficiency, gallstones and a marked susceptibility to infections are characteristic of this group of patients (7).

Hb H disease is the most severe, non fatal form of α-thal syndrome. This condition has long been thought to be a rather mild clinical condition since the majority of patients with Hb H have compensated hemolytic anemia with average Hb levels of more than 9.0 g/dL. However, hemolytic crises frequently develop often in the setting of acute infections (8).

It had been suggested that complications, particularly later in life, are less common in regularly transfused β-TI patients but more common in those that have undergone splenectomy (9).

The aim of the present study was to report the frequency of α- and β-TI among thalassemia patients registered at the Centre of Hereditary Blood Diseases (CHBD) in Basra, Southern Iraq, and the complications seen in these patients. The association between complications and risk factors such as age, type of thalassemia intermedia, splenectomy, frequency of blood transfusion and other factors was also investigated.

MATERIALS AND METHODS

This is a descriptive study carried out on patients with β-TI registered at CHBD in Basra, Southern Iraq, from October 1 2010 until July 1 2012. A total of 152 patients were recruited which represented all patients with β-TI registered at the center.

The ages of the patients ranged from 1 to 64 years; 104 (68.4%) were children and adolescents and 48 (31.6%) were adults. Males constituted 44.7% of the studied patients and females 55.3%. All of them were from Basra Province.

Patients with β-TI were diagnosed based on medical history, long intervals between transfusions or no need for any blood transfusions, as well as laboratory tests including complete blood count (CBC) and Hb electrophoresis, while the diagnosis of Hb H disease was made by the presence of Hb H on electrophoresis supplemented by demonstration of Hb H inclusions in red blood cells (1,6,10,11).

Clinical Assessment

Age, sex, age at diagnosis, age at first transfusion, number of blood transfusions per year, parental consanguinity, and family history of thalassemia were collected. Use of iron chelators, hydroxyurea (HU), heparin, aspirin, splenectomy and complications were also recorded. Full examination was made including growth parameters, pallor, jaundice, skin ulcers, and Tanner staging for sexual maturation (for pubertal patients).

Hematological Measurements

These included CBC and blood film. Hemoglobin electrophoresis was done by high performance liquid chromatography (HPLC) (VARIANT™, β- and α-Thalassemia Short Programs; Bio-Rad Laboratories, Hercules, CA, USA). Hb H preparation was done by incubating peripheral blood with methylene blue or brilliant cresyl blue. Smear examination showed red blood cells with Hb H inclusion bodies.

Iron Studies, Biochemical Tests and Densitometry

Iron overload was assessed by serum ferritin level measured by VIDAS (Biomerieux, Lyon, France) special immunoassay ELISA (enzyme-linked-immunosorbent serologic assay)-like system. Thyroid hormones (T3, T4, and TSH), gonadotropins (LH, FSH), alanine transaminase, and blood sugar were measured.

Echocardiography using VIVID S5 p mode colored Doppler (General Electric, Wauwatosa, WI, USA) was done for all patients. Radiological studies included X-ray and ultrasonography. In addition, computed tomography (CT) and contrast venography were done when indicated. Achilles in Sight (General Electric) ultrasonic calcanial bone densitometry was used.

Growth retardation was defined as body mass index (BMI) less than the 5th percentile and short stature with height less than the 3rd percentile (12-14). Complications such as extramedullary hematopoeisis (EMH), pulmonary hypertension (PHT), gallstone, leg ulcer, heart failure (HF), diabetes mellitus (DM), osteoporosis, deep vein thrombosis (DVT), and iron overload were also screened for. All complications were defined for all the recruited patients (8,15-17).

The study was approved by the Ethical Committee of Basra Medical College. An informed consent was obtained from patients and/or parents before enrollment in the study.

Statistical Analyses

Statistical analysis was done using SPSS program (Statistical Package for the Social Sciences version 17; Chicago, IL, USA). Comparisons of proportions were performed by crosstab using the χ^2 test. Logistic regression analysis was also performed for the analysis of different markers using analysis of variance (ANOVA). A p value of <0.05 was considered to be statistically significant.

RESULTS

Out of 942 patients with thalassemia registered at CHBD, 72 carried Hb H representing all registered α-thal patients. The remaining 870 were β-thal carriers, which included 790 with β-thal major (β-TM) and 80 with β-TI; β-TI constituted about 9.2% of the total number of patients with β-thal.

One hundred and fifty-two patients with Hb H and β-TI were included in this study. The predominant type (β-TI) was found in 80 (52.6%) patients; 104 (68.4%) of the patients were less than 18 years old, Table 1. In addition, β-TI was diagnosed at a significantly younger age (7.10 ± 8.0 years) than that of Hb H (12.95 ± 14.8 years, $p<0.05$) patients. A total of 54 (67.5%) of β-TI patients and 28 (38.8%) with Hb H were diagnosed between the ages of 2 and 5 years.

TABLE 1 Characteristics of 72 Patients With Hb H Disease and 80 Patients With β-Thalassemia Intermedia

Parameters	Hb H ($n = 72$) (47.4%)	β-TI ($n = 80$) (52.6%)	Total ($n = 152$) (100.0%)
Age (years)			
• <18	42 (58.3%)	62 (77.5%)	104 (68.4%)
• >18	30 (41.7%)	18 (22.5%)	48 (31.6%)
Sex			
• males	32 (44.4%)	36 (45.0%)	68 (44.7%)
• females	30 (55.6%)	44 (55.0%)	84 (53.3%)
Families with affected members	6 (8.3%)	8 (10.0%)	14 (9.2%)
Parental consanguinity	11 (15.3%)	16 (20.0%)	27 (17.8%)
Age (years) at diagnosis[a,b]	12.95 ± 14.80	7.10 ± 8.00	9.72 ± 11.76
• median	9	4	5
Blood transfusion frequency[a,b]	1.07 ± 1.39	3.39 ± 3.85	2.40 ± 3.24
History of blood transfusions	40 (55.6%)	63 (78.8%)	103 (67.8%)
Hb (g/dL)[a]	7.90 ± 0.99	7.31 ± 1.17	7.54 ± 1.12
Serum ferritin (ng/mL)[a,b]	765.0 ± 1054.0	2295.0 ± 2741.0	1698.9 ± 2340.0

[a]Variables are expressed as mean ± SD.
[b]p Value <0.05.

Hb H inclusions seen in red blood cells in children and adults with Hb H disease ranged from 9.0–96.0%. The mean percentage [± standard deviation (SD)] of Hb H for children was 7.85 ± 5.98; 5.83 ± 2.81 for males and 9.86 ± 7.44 for females. For adults, the mean Hb H value was 11.57 ± 8.95; 15.63 ± 11.55 for males and 8.52 ± 4.31 for females.

Concerning β-TI, the mean (± SD) Hb value was 7.31 ± 1.17 g/dL, MCV 66.36 ± 5.00 fL, MCH 20.06 ± 2.34 pg, and MCHC 29.96 ± 2.55 g/dL. On electrophoresis, the mean percentage (± SD) of Hb F was 53.02 ± 33.67%, Hb A_2 4.90 ± 1.10% and Hb A 21.75 ± 3.95%.

Out of 152 patients, 49 (32.2%) never received a blood transfusion including 32 (44.4%) with Hb H disease and 17 (21.2%) with β-TI. The mean serum ferritin level was significantly higher in patients with β-TI than those with Hb H disease, $p < 0.05$.

Growth retardation was the most common complication reported in patients with β-TI followed by short stature, iron overload, osteoporosis, and EMH. Heart failure, cholecystectomy, PHT and leg ulcers were less common complications.

Table 2 demonstrates that EMH, PHT, short stature and iron overload were significantly higher in patients with β-TI than patients with Hb H disease, and that cholecystectomy was significantly higher in patients older than 18 years compared with patients less than 18 years old, $p < 0.05$. Eighteen patients were splenectomized, and most complications were significantly higher in splenectomized patients compared to non splenectomized patients, except for osteoporosis, and other complications such as gallstones, DVT and leg ulcers, where the number of patients with these complications was small (Table 3).

TABLE 2 Complications of the Studied Patients in Relation to the Type of Thalassemia Intermedia and Age

Complication	α-TI ($n = 72$)	β-TI ($n = 80$)	Total ($n = 152$)	p Value	<18 years ($n = 104$)	>18 years ($n = 48$)	Total ($n = 152$)	p Value
	n (%)	n (%)	n (%)		n (%)	n (%)	n (%)	
Short stature	16 (22.2)	34 (42.5)	50 (32.9)	0.010				
Growth retardation	25 (34.7)	40 (50.0)	65 (42.8)	0.104				
Osteoporosis	13 (18.0)	24 (30.0)	37 (24.3)	0.083	25 (24.0)	12 (25.0)	37 (24.3)	0.490
Extramedullary hematopoiesis	4 (5.6)	14 (17.5)	18 (11.8)	0.042	13 (12.5)	5 (10.4)	18 (11.8)	0.620
Heart failure	0 (0.0)	11 (13.8)	11 (7.2)		7 (6.7)	4 (8.3)	11 (7.2)	0.152
Pulmonary hypertension	1 (1.4)	4 (5.0)	5 (3.5)	0.020	2 (2.0)	3 (6.3)	5 (3.3)	0.157
Gallstones	1 (1.4)	2 (2.5)	3 (2.0)		0 (0.0)	3 (6.3)	3 (2.0)	
Cholecystectomy	0 (0.0)	6 (7.5)	6 (4.0)		1 (1.0)	5 (10.4)	6 (4.0)	0.007
Deep vein thrombosis	0 (0.0)	2 (2.5)	2 (1.3)		0 (0.0)	2 (4.1)	2 (1.3)	
Leg ulcers	1 (1.4)	3 (3.8)	4 (2.6)		2 (2.0)	2 (4.1)	4 (2.6)	
Iron overload	8 (11.1)	36 (45.0)	44 (28.9)	0.009	32 (30.8)	12 (25.0)	44 (28.9)	0.110

Out of 152 patients, 44 (28.9%) β-TI patients had iron overload. Short stature, growth retardation, osteoporosis, EMH and HF were statistically significantly higher in patients with iron overload compared with patients without iron overload, $p < 0.05$ (Table 3).

TABLE 3 Complications of the β- and α-Thalassemia Intermedia Patients in Relation to Splenectomy and Iron Overload

Complication	Splenectomy		Total		Iron Overload		Total	
	$n = 18$	$n = 136$	$n = 152$	p Value	$n = 44$	$n = 108$	$n = 152$	p Value
	Yes n (%)	No n (%)	n (%)		Yes n (%)	No n (%)	n (%)	
Short stature	12 (66.7)	38 (27.9)	50 (32.9)	0.042	37 (84.1)	13 (12.0)	50 (32.9)	0.016
Growth retardation	12 (66.7)	53 (39.0)	65 (42.8)	0.019	42 (95.5)	23 (21.3)	65 (42.8)	0.021
Osteoporosis	6 (33.3)	31 (39.0)	37 (24.3)	0.181	16 (36.4)	21 (19.4)	37 (24.3)	0.041
Extramedullary hematopoiesis	8 (44.4)	10 (7.4)	18 (11.8)	0.033	9 (20.5)	9 (8.3)	18 (11.8)	0.032
Heart failure	6 (33.3)	5 (3.7)	11 (7.2)	0.021	8 (18.2)	3 (2.8)	11 (7.2)	0.027
Pulmonary hypertension	2 (11.1)	3 (2.2)	5 (3.3)	0.034	2 (4.5)	3 (2.8)	5 (3.3)	0.052
Gallstones	1 (5.6)	2 (1.5)	3 (2.0)		2 (4.5)	1 (0.93)	3 (2.0)	
Cholecystectomy	5 (27.8)	1 (0.74)	6 (4.0)	0.019	6 (13.6)	0 (0.0)	6 (4.0)	
Deep vein thrombosis	2 (11.1)	0 (0.0)	2 (1.3)		1 (2.3)	1 (0.93)	2 (1.3)	
Leg ulcers	3 (16.7)	1 (0.74)	4 (2.6)		2 (4.5)	2 (1.9)	4 (2.6)	
Iron overload	10 (55.6)	34 (25.0)	44 (28.9)	0.028				

TABLE 4 Logistic Regression Analysis of Different Variables With Complications in Both Types of Thalassemia Intermedia

Variable	OR	95% CI	*p* Value
α-Thalassemia Intermedia[a]			
Iron overload	2.252	1.082–8.202	<0.05
Splenectomy	2.655	0.818–13.595	>0.05
Osteoporosis			
Iron overload	0.963	0.482–3.681	>0.05
Splenectomy	0.706	0.269–3.333	>0.05
Age	1.366	1.108–6.562	<0.05
β-Thalassemia Intermedia			
Iron overload	3.920	1.113–8.102	<0.05
Splenectomy	4.521	0.902–10.320	>0.05
Osteoporosis			
Iron overload	1.106	0.726–3.122	>0.05
Splenectomy	0.992	0.328–3.286	>0.05
Age	2.706	1.332–7.062	<0.05
Extramedullary Hematopoiesis			
Iron overload	1.282	0.403–4.436	>0.05
Splenectomy	14.811	4.048–59.803	<0.001
Age	0.765	0.208–2.432	>0.05
Heart Failure			
Iron overload	23.440	2.301–238.740	<0.01
Splenectomy	12.245	2.069–72.481	<0.01
Age	3.260	0.472–22.471	>0.05

OR: odds ratio; 95% CI: 95% confidence interval.

None of the patients with α-TI suffered heart failure and only four patients had extramedullary hematopoeisis; both types of thalassemia intermedia suffered from growth retardation.

Selected variables were subjected to logistic regression analysis to ascertain which of them were significantly associated with growth retardation, osteoporosis, EMH, and HF in both types of thalassemia intermedia. Mean serum ferritin level of more than 1000 μg/L was associated with an increased risk of growth retardation among patients with both types of thalassemia intermedia and significantly associated with HF in patients with β-TI. Splenectomy was associated with an increased risk of EMH and HF in patients with β-TI, while increased age was associated with an increased risk of osteoporosis in both types of thalassemia intermedia (Table 4).

DISCUSSION

Great strides have been made in the care of patients with β-TM due to improved transfusion strategies, safer blood products, the use of cardiac magnetic resonance (CMR) for assessing cardiac iron loading, improved

methods of chelation, and the use of allogeneic bone marrow transplantation (18,19). Much less is known about less severe forms of thalassemia in terms of frequency, management and complications.

Thalassemia is common in Arab countries and many neighboring countries. For example, in Tunisia β-thal is the predominant Hb abnormality (2.21%) and the frequency of the α-thal genes is 5.48% (20), while in Jordan, the carrier rates for β-, α-thal and sickle cell anemia are in the range of 2.0–4.0% (21). The frequency of β-thal in these countries is lower than that reported in different areas of Iraq including Basra (3–5).

Consanguineous marriages are common in most communities of the Middle East, where intra-familial unions collectively account for 20.0–50.0% of all marriages (22). In Iraq, the percentage of consanguineous marriages range from 40.0–49.0%, and the percentage of first cousin marriages is around 28.0% (23,24).

The majority of patients with β-TI in this study were less than 18 years old. This can be attributed to increased awareness, and improved diagnosis and care for patients with this type of thalassemia during the past few years. In a multi center study in Lebanon, Italy, Iran, Egypt, United Arab Emirates and Oman, the mean age for patients with β-TI was 25.44 ± 13.86 years (range 2–76 years), which is much higher than that reported from our center (15).

The CHBD is the only center caring for patients with hemoglobinopathies in Basra. As the fully functioning center has only recently been established, we do not have an estimation of previous mortality and survival. Therefore, it is difficult to conclude whether the low rate of patients older than 18 years is a reflection of selective mortality or differential coverage of patients attending the CHBD. In addition, there are no preventive measures for thalassemia such as premarital screening in most parts of Iraq including Basra, and prenatal diagnosis and termination of pregnancy with affected fetus are restricted by legal and religious limitations. These preventive measures are very important because of the cost and difficulties in providing optimal treatment for patients, and the innumerable fatalities from untreated β-thal.

The present study has revealed that mean age at diagnosis of α-TI and β-TI differs significantly as β-TI was being diagnosed at a significantly younger age. This is in agreement with many studies which reported that β-TI is diagnosed earlier than α-TI (8,11); this might be attributed to the severity of the disease. The pattern of α-TI, assessed by the percentage of Hb H and Hb level, reported in the present study is comparable to that reported by Ankra-Badu *et al.* (25) and Qadri and Islam (26) in two regions in Saudi Arabia and by Venugopal *et al.* (27) in Oman.

Growth retardation and short stature were reported in more than one-third of patients with thalassemia intermedia, with a higher percentage among β-TI compared to α-TI. Short stature was reported in 46.0% of Iranian patients with β-TI (28), while other reports gave growth retardation

a range of 13.0–21.0% in patients with Hb H (29,30). This can be attributed to more blood transfusions and iron overload and iron-induced damage to the hypothalamic pituitary axis, which can cause delayed pubertal growth and sexual development even with timely initiation of iron chelation in early childhood (11).

Pulmonary hypertension was found in very low percentages in patients with β-TI compared with other studies where PHT ranges between 11.0–59.0% (15,16,31). This could be attributed to the younger age of patients included in this study compared to these studies.

Patients with iron overload were reported to have increased frequency of complications including growth retardation, short stature, osteoporosis, EMH and HF. Rachmilewitz *et al.* (11) and Taher *et al.* (9,15) reported that iron overload was independently associated with growth retardation and HF in patients with β-TI, which is in agreement with the results of the current study.

Increased complications among patients with iron overload were mainly due to the toxic effects of free iron radicals. Iron chelation therapy was protective for many complications including growth retardation, hypogonadism, PHT, cholelithiasis, and osteoporosis (15).

In the present study, patients with β-TI had higher mean serum ferritin levels than patients with α-TI. It was reported that iron overload is uncommon in patients with Hb H from the Mediterranean region. Although unrelated to previous history of transfusions, iron overload could be related to genotype; patients with nondeletional Hb H disease have more symptoms at a younger age, more severe hemolytic anemia, more growth deficiency, higher serum ferritin levels and require more transfusions than patients with deletional Hb H disease (29,30). However, one of the limitations of this study is that molecular analysis was not done for these patients.

Age was found to be an independent risk factor for osteoporosis in patients with Hb H disease and β-TI in the current study. These results are similar to those reported by other researchers concerning both types of thalassemia intermedia (9,32,33).

Splenectomy was found to be independently associated with increased risk of EMH and HF in patients with β-TI in the current study. Almost all complications were reported in a higher frequency among splenectomized patients compared with non splenectomized patients; many studies reported a similar finding (8,15,31). Taher *et al.* (9) reported an independent role for splenectomy in a higher occurrence of thromboembolism, PHT, HF, EMH, leg ulcers, and iron-related endocrinopathy. The development of these complications has been related to the presence of high platelet counts and aggregation after splenectomy and/or to an increased number of RBCs with negatively charged membranes that carry thrombogenic potential (8,15).

Leg ulcers are more common in older than in younger patients with β-TI. The skin at the extremities of elderly β-TI patients can be thin due to

reduced tissue oxygenation, and this makes the subcutaneous tissue fragile and increases the risk of lesions from minimal trauma. Although blood transfusions and short-term treatment with HU or recombinant human erythropoietin have been shown to favor ulcer healing. In most cases the ulcers recur when therapy is discontinued (34).

CONCLUSIONS

As both Hb H disease and β-TI are reported in patients with thalassemia and with considerable complications among them both, genetic studies to determine the types of mutation producing β-TI and the exact α-thal determinants producing Hb H disease are needed in Basra as well as other parts of Iraq, which are important in the prediction of the phenotype severity.

ACKNOWLEDGMENTS

We would like to thank Dr. Sadeq Khalif Ali, a hematologist at the Centre for Hereditary Blood Diseases, Basra, Southern Iraq, for his great help in the laboratory investigations and Professor Assad Yehia, College of Agriculture, Basra, Southern Iraq, for his assistance in the statistical analyses of the data.

Declaration of Interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

REFERENCES

1. Giardina PJV, Forget BG. Thalassemia syndromes. In: Hoffman R, Shattil SJ, Furie B, Silberstein LE, McGlave P, Eds. Hoffman Hematology: Basic Principles and Practice, 5th ed. Philadelphia: Churchill Livingstone. 2008:606–632.
2. Modell B, Darlison M. Global epidemiology of hemoglobin disorders and derived service indicators. Bull World Health Organ. 2008;86(6):480–487.
3. Al-Allawi NA, Al-Dousky AA. Frequency of haemoglobinopathies at premarital health screening in Dohuk, Iraq: implications for a regional prevention programme. East Med Health J. 2010;16 (4):381–385.
4. Yahya HI, Khalel KJ, Al-Allawi NA, Helmi F. Thalassaemia genes in Baghdad, Iraq. East Med Health J. 1996;2(2):315–319.
5. Hassan MK, Taha JY, Al-Naama LM, Widad NM, Jasim SN. Frequency of haemoglobinopathies and glucose-6-phosphate dehydrogenase deficiency in Basra. East Med Health J. 2003;1(2):1–9.
6. Adams RJ, Brambilla D. Genetic disorders of hemoglobin. In: Hoffbrand AV, Moss PA, Pettit IE, Eds. Essential Hematology, 5th ed. Malden: Blackwell Publishing Company. 2006:72–84.
7. David J. Hemoglobin and the inherited disorders of globin synthesis. In: Hoffbrand AV, Catovsky D, Tuddenham EG, Eds. Postgraduate Hematology, 5th ed. Malden: Blackwell Publishing Company. 2005:85–89.
8. Fucharoen S, Viprakasit V. Hb H disease: clinical course and disease modifiers. Hematology Am Soc Hematal Educ Program. 2009:26–34.
9. Taher A, Musallam KM, Cappellini MD. Optimal management of thalassaemia intermedia. Br J Haematol. 2011;152(5):512–523.

10. Camaschella C, Cappellini MD. Thalassemia Intermedia. Haematologica. 1995;80(1):58–68.
11. Rachmilewitz EA, Giardina PJV. How I treat thalassemia? Blood. 2011;118(13):3479–3488.
12. National Center for Health Statistics Centers for Disease Control (CDC). PedNSS Health Indicators. 2009. http://www.cdc.gov/pednss/what_is/pednss_health_indicators.html (accessed February 7 2012.)
13. Krebs NF, Primak LE. Obesity. In: Kliegman RM, Jenson HB, Marcdante KJ, Behrman RE, Eds. Nelson Essentials of Pediatrics, 5th ed. Philadelphia: Elsevier Saunders. 2006:140–142.
14. Kushner RF. Evaluation and management of obesity. In: Fauci AS, Braunwald E, Kasper DL, Hauser SL, Longo DL, Jameson JL, Eds. Harrison's Principles of Internal Medicine, 17th ed. New York: McGraw-Hill Companies. 2007:468–472.
15. Taher A, Musallam KM, Karimi M, *et al.* Overview on practices in thalassemia intermedia management aiming for lowering complication rates across a region of endemicity: the OPTIMAL CARE study. Blood. 2010;115(11):1886–1893.
16. Cappellini MD, Musallam KM, Taher A. Thalassemia Intermedia an update. Mediterr J Hematol Infect Dis. 2009;1(1):625–31.
17. McKee PA, Castelli WP, McNamara PM, Kannel WB. The natural history of congestive heart failure: the Framingham study. N Engl J Med. 2002;285 (26):1441–1446.
18. Cappellini MD, Musallam KM, Cesaretti C, Taher A. Thalassemia intermedia. In: Beaumont C, Beris P, Beuzard Y, Brugnara C, Eds. Disorders of Erythropoiesis, Erythrocytes and Iron Metabolism. Genoa: Forum Service Editore. 2009:286–309.
19. Modell B, Khan M, Darlison M, Westwood MA, Ingram D, Pennell DJ. Improved survival of thalassaemia major in the UK and relation to T2* cardiovascular magnetic resonance. J Cardiovasc Magn Reson. 2008;10(1):42.
20. Fattoum S. Evolution of hemoglobinopathy prevention in Africa: results, problems and prospect. Mediterr J Hemat Infect Dis. 2009;1(1):e2009005.
21. Hamamy H, Al-Hait S, Alwan A, Ajlouni K. Jordan: communities and community genetics. Community Genet. 2007;10(1):52–60.
22. Hamamy H. Consanguineous marriages; preconception consultation in primary health care settings. J Community Genet. 2012;3(3):185–192.
23. Alwan A, Modell B. Community control of genetic and congenital disorders. World Health Organization. Eastern Mediterranean Regional Office Technical Publication, Series 24. 1997:64–66.
24. www.consang.net/global prevalence. Accessed January 6 2013.
25. Ankra-Badu GA, Al-Jama A, Al Kadim Y. Hemoglobin H disease in the AL-Qatif region of Saudi Arabia. Ann Saudi Med. 2001;21(5–6):308–311.
26. Qadri MI, Islam SA. Hemoglobin H disease in the eastern region of Saudi Arabia. Saudi Med J. 2000;21 (7):666–671.
27. Venugopal S, Dhuri S, Al Jabal KB, Shaju A. Hemoglobin H disease in Muscat, Oman – A 5 year study. Oman Med J. 2008;23(2):82–85.
28. Karamifar H, Karimi M, Amirhakimi GH, Badiei M. Endocrine function in thalassemia intermedia. Int J Biomed Sci. 2006;2(3):236–340.
29. Chui DHK, Fucharoen S, Chan V. Hemoglobin H disease: not necessarily a benign disorder. Blood. 2003;101(3):791–800.
30. Laosombat V, Viprakasit V, Chotsampancharoen T, *et al.* Clinical features and molecular analysis in Thai patients with Hb H disease. Ann Hematol. 2009;88(12):1185–1192.
31. Cappellini MD, Robbiolo L, Bottasso BM, Beuzard Y. Venous thromboembolism and hypercoagulability in splenectomized patients with thalassaemia intermedia. Br J Haematol. 2000;111(2):467–473.
32. Taher AT, Musallam KM, El-Beshlawy A, *et al.* Age-related complications in treatment – naïve patients with thalassaemia intermedia. Br J Haematol. 2010;150(4):480–497.
33. Vichinsky E. Complexity of α thalassemia: growing health problem with new approaches to screening, diagnosis, and therapy. Ann NY Acad Sci. 2010;1202:180–187.
34. Aessopos A, Kati M, Tsironi M, Polonifi E, Farmakis D. Exchange blood transfusions for the treatment of leg ulcerations in thalassemia intermedia. Haematologica. 2006;91(3):e37–e38.