B- THALASSEMIA MAJOR IN RAMADI

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Summary:

Fac Med Baghdad 2005; vol.47 No. 2
Received:Jan. 2004
Accepted: March 2005

Background: *The thalassemias are a heterogeneous group of genetic disorders in which the production of normal hemoglobin is partly or completely suppressed because of a defective synthesis of one or more globin chain_In Iraq, B - thalassemia major is widely distributed all over the country.*
An active program for the hereditary blood diseases had been adopted in cooperation with WHO in 1989. This study is done to evaluate the burden of the disease and its treatment on thalassemic patients in Ramadi.
Methods: *_Thirty-one children with B- thalassemia major (17 males and 14 females) aged 9 months- 21 years attending the thalassemic clinic in MCH in Ramadi during the period from 1st Dec. 2001 to 31st May 2002 were studied prospectively. _History, clinical examination , investigations ,treatment and its complications were noted and analysed . Statistical analysis was done by the use of SD, t-test and P value of <0.05was considered statistically significant.*
Results: *90% had pretransfusion Hb <9gm/ dl. Only 27% received Desferal regularly subcutaneously by infusion pumps. Splenectomy was done in 19.3%, all of them received pneumococcal vaccine and half of them received Benzathine penicillin regularly monthly. Body weight and height below 3rd percentile were noticed in 22.5% and 32.2% respectively. About 32% had myocardial systolic or diastolic dysfunction detected by Doppler echocardiography. Non had hypocalcemia. HBs Ag positive in 6.4%. Anti HCV was positive in 12.5%.None was positive for HIV.*
Conclusions: *_The majority of patients were undertreated and various complications were probably related to chronic anemia rather than iron overload.*

Introduction

The thalassemias are a heterogeneous group of genetic disorders in which the production of normal hemoglobin is partly or completely suppressed because of a defective synthesis of one or more globin chain [1].

It has been estimated that there are probably as many as 100000 living patients with homozygous *B*- thalassemia in the world [2].

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B-thalassemia occurs most frequently in the Mediterranean and Middle East regions, Iran, Pakistan, India and China. The incidence of *B*-thalassemia gene frequency in these countries is in range of 2-25% [3].

Regular RBC transfusions eliminate the complications of anemia and compensatory bone marrow expansion; permit normal development through out childhood, and extend survival [4] . In parallel transfusion results in a second disease while treating the first, that of inexorable accumulation of tissue iron, without treatment it is fatal in the second decade of life [5] .

Iron chelating therapy by Deferoxamine mesylate, first introduced in 1966 gained acceptance as a standard therapy in countries able to support the high cost of this therapy [6] .

In Iraq, B - thalassemia major is widely distributed all over the country. The highest number registered cases are 1241 in Baghdad and the lowest in Sala Aldin 19 cases.

An active program for the hereditary blood diseases had been adopted in cooperation with WHO in 1989. Thalassemia clinics and wards had been established in all governorates, their goals are regular follow up, proper management, early detection and education of patients and their families.This study is done to evaluate the burden of the disease and its treatment on thalassemic patients in Ramadi.

METHODS:

Thirty-one children with B-thalassemia major followed in thalassemic clinic in MCH in Ramadi were studied in the period from 1st Dec. 2001 to 31st May 2002.

Data recorded were: age, sex, consanguinity, family history of thalassemia, symptoms like abdominal pain, bone pain and numbness. Clinical examination was performed for height, weight, skin color dysmorphic features, hepatosplenomegaly. Investigations were done like abdominal ultrasound, echocardiographs, S. Ferritin, S.Ca, S. Ph, S.Alk .Ph, HBs Ag, Anti HCV and Anti HIV antibodies.

Frequency of blood transfusion, pretransfusion Hb, desferal therapy, the use of infusion pumps, splenectomy, use of folic acid, vitamin C, pneumococcal vaccine, prophylactic antibiotics were recorded .

Statistical analysis was done by the use of SD, t-test and P value of <0.05was considered statistically significant.

RESULTS:

There were 31 thalassemic patients attending the thalassemic clinic in MCH in Ramadi, their age range was from 9 months to 21 years with a mean age of 8.35 years. 17(54.8%) were males and 14(45.2%) were females (Table-1). The clinical features of thalassemic patients are summarized in Table-2. Table- 3 shows progressive stunting of growth with advancing age.

Thirteen (42%) patients were attending the thalassemic center for blood transfusion during the study period presented with Hb <7 gm / dl, while 15(48%) of them their Hb ranged from 7-9 gm/ dl before transfusion and only 3 (9.7%) had pre-transfusion Hb>9 gm /dl.

The levels of S.Ca, S. Ph., S.Alk. Phosphatase and S. Ferritin (mean +SD) according to age group are described in Table-4. Hypocalcemia was not recorded and the mean serum Ferritin was 889.68 ng/ml.

By echocardiographic examination,six (19.3%) patients showed myocardial systolic dysfunction started at the age of 9-12 years, while 4(12.5%) showed diastolic dysfunction started at the age of 12-15 years. These abnormalities were shown to have a statistically significant association with advancing age, but no correlation was detected between S.Ferritin and echo abnormalities (Table-5).

The positive sera for HBsAg were 2(6.4%) and for anti HCV antibodies were 4(12.5%). None was positive for HIV (Table-6).

Desferal was taken by 26(83.2%), while 5 (15.8%) did not receive desferal at all. From those who received desferal 17 (65.4%) patients received it as intramuscular injection on irregular bases and 2(7.7%) as single intravenous infusion with blood transfusion, and 7(27%) received the drug subcutaneously using small portable infusion pumps.

None of the patients received folic acid regularly, and only one received vitamin C tablets regularly with desferal infusion.

Splenectomy was done for 6(19%) patients. Three of them (50%) received benzathine penicillin every 4 weeks, and all of them received pneumococcal vaccine.

Table-1: Age and sex distribution of 31 thalassemic children

Age(years)	Males		Females		Total	
	No.	%	No.	%	No.	%
<3	2	6. 24	2	6.24	4	13
3<6	4	12.4	4	12.4	8	25.8
6<9	3	9.3	0	0	3	9.6
9<12	4	12.4	4	12.4	8	25.8
12<15	1	3.22	3	9.3	4	12.8
15<18	2	6.24	0	0	2	6.4
18-21	1	3.22	1	3.22	2	6.4
Total	17	54.8	14	45.2	31	100

Table -2:Clinical features of 31 thalassemic children

Clinical features	No.	%
Bronzy skin	22	70.7
Facial disproportion	19	61.3
Splenomegaly>5cm	16	64
Hepatomegaly>5cm	20	64.5
Abdominal pain	5	16

Table-3: Weight and height in thalassemic children

Age (Years)	Total No.	Wt/Age<3rd centile		Ht/Age <3rd centile	
		No.	%	No.	%
<3	4	0	0	0	0
3<6	8	1	3.22	0	0
6<9	3	0	0	0	0
9<12	8	0	0	3	9.3
12<15	4	2	6.45	3	9.3
15<18	2	2	6.45	2	6.45
18-21	2	2	6.45	2	6.45
Total	31	7	22.5	10	31.5

Table-4: Biochemical profiles of 31 thalassemic children

Age (years)	S.Ca (mg/dl)	S.Ph (mg/dl)	S.Alk. Phos.K.A.U.	S.Ferritin (ng/ml)
<3	9±1.51	5.78±1.65	16.00±0.00	817.50±236.13
3<6	9.43±1.49	5.68±1.26	14.40±1.18	965.00±240.77
6<9	9.97±1.05	6.63±2.12	15.50±6.36	778.33±50.08
9<12	9.3±172	6.86±1.88	20.25±7.87	966.25±155.19
12<15	9.25±0.5	7.5±3.00	19.75±3.30	933.75±80.97
15<18	10.25±1.06	7.15±4.03	18.38±2.2	790.00±236.98
18-21	9.9±0.99	7.05±4.17	11.50±2.12	605.00±275.77

Table-5: Echocardiographs abnormalities in thalassemic patients

Age (Years)	*Echo. abnormalities		Systolic dysfunction		Diastolic dysfunction	
	No.	%	No.	%	No.	%
<3	-		-		-	
3<6	-		-		-	
6<9	-		-		-	
9<12	3	9.3	3	9.3	-	
12<15	4	12.3	2	6.45	2	6.45
15<18	1	3.22	-		1	3.22
18-21	2	6.45	1	3.22	1	3.22
Total	9	29	6	19.4	4	12.4

*P<0.05 with advancing age

Note: No correlation was detected between S.Ferritin and echo abnormalities

Table -6: Viral hepatitis infection in 31 thalassemic children

Age (Years)	Total No.	Anti-hepatitis C antibodies		HBs Ag	
		No.	%	No.	%
<3	4	-		-	
3<-6	8	-		-	
6<9	3	1	3. 22	-	
9<12	8	2	6.45	-	
12<15	4	1	3.22	1	3.22
15<18	2	-		1	3.22
18-21	2	-		-	
Total	31	4	(12.4%)	2	(6.4%)

Table-7: Number of thalassemic children registered in thalassemic clinics in the centers of different governorates

Thalassemic center	No.	Thalassemic center	No.
Baghdad	1241	Taamim	178
Mosul	582	Thikar	113
Basrah	561	Najaf	64
Diala	215	Muthanna	46
Wasit	199	Anbar	31
Babel	195	Salah -Aldin	19

DISCUSSION:

A survey conducted in the year 2000 on primary school children revealed a prevalence of *B*-thalassemia trait in Ramadi of 0.062% (7). It was lower than that recorded in Baghdad (4.4%). and Basrah (20%) [8] . Some thalassemic children from Ramadi province were registered in thalassemic centers in Baghdad for more facilities available there.

Male predominance was noticed in this study and many other studies but no explanation was given for this difference [9,10,11] .

Typical cephalofacial disproportions were observed in 61.3% of patients, which is higher than that recorded in Baghdad (54%) [11] . This finding is expected since the majority was undertranfused.

Both weight and height were markedly reduced below 3rd centile in 22.5% and 32.2% respectively, but these results are much lower than those reported by Al-Hadiari (48.5%) and (64.7%) respectively [10] .

The key contributing factors to stunted growth in patients with *B*- thalassemia major may include chronic anemia, hypogonadism and chelating toxicity [3] .

Lack of effective chelation therapy is probably the reason for this percent of growth failure.

Gabriele first described hypoparathyroidism secondary to siderosis in thalassemic patients in 1971 [16] , and the prevalence of hypocalcemia

varied greatly from very low to as high as 29.5% [17].

Using low S.Ca. and S.Ph., normal S.Alk. Ph. and low parathyroid hormone level as a base for the diagnosis of hypoparathyroidism, none of the studied cases had hypoparathyroidism. Different results were recorded in Baghdad (21.3%) [18], and Italy (4.5%) [20].

This result may be explained by the fact that almost all patients who had hypocalcemia in other studies were over 10 years of age [21], while 48% of the patients in this study were under 10 years of age.

Mild iron overload (mean S. Ferritin 889.96 ng/ml) was noted in all studied children. This is in agreement with a study done in Saudi Arabia (800ng/ml), but in contrast with an other study performed in the same country (3965ng/ml) [9]. This finding can be attributed to undertransfusion rather than to effective chelatng therapy.

Echocardiographs characteristics in patients with *B*-thalassemia major were extensively studied and debated [23,24,25].

In general with increased iron loading, indices of systolic function, cardiac dimension and myocardial wall thickness is normal until unequivocal symptoms of CHF are apparent [26].

In this study left ventricular systolic dysfunction appeared in early phase of the disease before the appearance of diastolic dysfunction in the absence of clinical features of heart failure, but early diastolic dysfunction was recorded in an other study in Turkey [27].

In addition to Serum Ferritin level, which showed no correlation with echocardiographs changes different mechanisms have been postulated including individual sensitivity to iron damage and chronic anemia [25].

Thalassemia major is a known risk factor for blood born infections. 21.5% of cases were seropositive for Anti HCV Antibodies and 6.4% for HBsAg, while none for Anti HIV Antibodies. A recent study in Diala showed almost`similer findings (14.5% of cases were seropositive for Anti HCV Antibodies and 3.6% for HBsAg) [28], but in India 66.6% of cases were seropositive for Anti HCV Antibodies and 7.4% for HBs Ag [29].

Direct communication with Central Health Lab. reviled 10%of cases were seropositive for Anti HCV Antibodies and 0.2% for HBsAg, while none for HIV. The lower results can be attributed to low prevalence of Anti HCV Antibodies and HBs Ag in Ramadi province.

Ninety percent of patients received blood transfusion at a Hb level < 9 gm /dl, so the majority were in a low transfusion regimes, and this may be due to some difficulties in obtaining blood and the psychosocial state of the parents. Maintenance of Hb level >10 gm/dl is good in leading normal life activity and make complications more little [4,13,14,15]

Only 27% received desferal regularly subcutaneosly through infusion pumps, while the majority received the drug by intramuscular or intravenous routs with blood transfusion or not receive it at all. Intramuscular or intravenous injections of desferal are not effective and proved disappointing, as the amount of iron excreted is barely sufficient to obtain negative iron balance [12]

Poor compliance, unavailability of pumps and free blood transfusions may be the main causes for improper desferal therapy.

Conclusions from this study include that the majority of thalassemic patients in Ramadi are undertreated and various complications probably related to chronic anemia rather than iron overload.

Recommendations include free blood donation, availability of infusion pumps, vaccination by hepatitis -B and pneumococcal vaccine, folic acid and vitamin- C supplementation, Prophylactic benzathine penicillin for splenectomized patients. Regular checking for growth parameters, health education, genetic counseling should be offered to all families of thalassemic children.

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