Study of growth retardation among patients with thalassemia major: correlation to iron overload

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Abstract

Thalassemia is an autosomal recessive blood disorder which has a life-long implication in both patients and their families. This study was performed at Al-Diwaniya maternity and children teaching hospital from the 1st of October 2016 to the 1st of January 2017. The total number of patients involved in our study were one-hundred three, all of them were diagnosed with ß - thalassemia major, were subjected to frequent blood transfusion and were on chelating agent. Both patients groups were evaluated with full history (age, gender, time of diagnosis, the rate of transfusion per year, the type and dose of the chelating agent), and were examined for their weight, height and BMI, serum ferritin was also performed for all of them. There was a significant difference in mean age and height of patients on desferal and those on exjade. The rate of transfusion was significantly greater in the group of patients treated with desferal. Serum ferritin was significantly higher in patients treated with desferal than patients treated with exjade. There was a significant correlation between gender of patients and serum ferritin in the group of patients treated with desferal, also there was a significant negative correlation between the dose of the drug and serum ferritin in those treated with exjade.

Keywords: Growth retardation; Thalassemia; Desferal

Introduction

Thalassemia refers to a group of inherited heterogeneous disorder of hemoglobin production due to defective globin gene, resulting in numerous quantitative defects in B- globin production and decreased production (ß$^+$ thalassemia), or complete absence of B-globin chain (ß^0 - thalassemia) [1]. Beta-thalassemia major (BTM) is usually presented in early months of life (4 - 6 months of life), because of high hemoglobin F level in early life prevents the appearance of hemolysis early but when there is slowly

decline in hemoglobin F level during the first year of life, variable degrees of anemia presented [2]. The required treatments for thalassemia major include frequent blood transfusion (every 2-5 weeks) to keep Hb – level before transfusion above 9-10.5 gm/dl and Hb – level after transfusion should not be more than 14-15 gm/dl [3], obtain normal growth and development and suppress the erythroid hyperplasia and skeletal abnormalities [3,4]. Each unit of packed red cells contain 200-240 mg of iron so that Chronic blood transfusion in Beta-thalassemia major patients lead to accumulation of iron in the body and leads to many complications especially growth retardation ,failure or delay of sexual maturation, the heart (dilated cardiomyopathy or rarely arrythmias), liver (fibrosis and cirrhosis), endocrine glands (diabetes mellitus, hypogonadism, hypoparathyroidism and sometime adrenal glands insufficiency) [5]. Growth retardation in Beta-thalassemia major patients is presented in two forms: height worrisome (short stature) and velocity worrisome (growth failure). Short stature and growth failure frequently but not always occur together [6]. Linear growth is considered retarding when firstly a person height cross more than 2 standard deviation below the mean height for age and sex or height below 3th centile for age and sex and secondarily when a person linear growth velocity decreased to less than 4cm / year or when person growth informs widely deviate from that of parents [7, 8]. Growth retardation in ß – thalassemia major children can appear early in 1st two years of life but signs of growth retardation are more apparent after the 6-8 years of life. But with optimal blood transfusion therapy, growth and development stayed normally until 10 to 12 years [9, 10]. The cause of growth retardation has long been a subject of debate [11]. Normal growth can be maintained by preventing chronic tissue hypoxia and this can be performed by maintaining Hb above 9 together with adequate iron chelation [11]. Iron chelating should start as the patient become significantly iron overloaded, in general this occur after 1 year of transfusion therapy and correlate with s. ferritin > 1000 ng /ml [1].

Aims of the study

This study was adopted to determine; the correlation of growth retardation with certain variable factors including the age, the gender of the patient, the age at time of diagnosis of, the number of blood transfusions per year, serum ferritin, the type of chelating

agent; the efficacy of exjade (deferasirox) in decreasing iron overload in comparison to that of deferoxamine, with its consequence on growth.

Patients and methods

This study was performed at Al- thalassemia center of Al-Diwaniya maternity and children teaching hospital from the 1st of October 2016 to the 1st of January 2017. Total number of patients involved in our study were 103 (46 male and 57 female), all of them were diagnosed with ß – thalassemia major, they were subjected to a frequent blood transfusion and were kept on chelating agents. Those patients were checked and were followed during their regular visits and they classified in to two major groups (according to the type of chelating agent used for them) , oral permissions were obtained from all patients to be involved in the study. Both patients groups were evaluated with a full history (the age , the gender, the time of diagnosis, the rate of transfusions per year , the type and dose of chelating agent) , and were examined for their weight , height and BMI (normal BMI= 18.5-24.9, < 18.5 is considered underweight, 25- 29.9 is overweight), these measurements were done by one examiner, s.ferritin was also performed for all of them.

Statistical analysis

Data were analyzed using SPSS version 23 and Microsoft office excels 2010. Numeric variables were expressed as mean and standard deviation, whereas, categorical variables were expressed as number and percentage. Chi-square test was used to study the association between categorical variables, student t-test was used to study the difference in mean numeric variables between any two groups and Spearman correlation was used to investigate correlations among numeric variables in the two study groups. P-value was considered significant at P≤0.05.

Results

General characteristics of the study group are shown in table 1. This study includes 103 thalassemic patients, 46 males and 57 females. Mean age was 14.51±5.78 years. Mean age at time of diagnosis was 1.28 years. Mean transfusion rate was 18.57 ± 5.77 pint per year. Mean BMI was ranging from 9.96 to 38.52 and averaged 17.50 ± 4.81 kg/m^2. Mean serum ferritin was 4623.20 ± 304.42.

Table 1.

Characteristics of all thalassemia patients were enrolled in the study.

Characteristic	N	Mean	SD	Minimum	Maximum
Age of patient (years)	103	14.51	5.78	1.00	36.00
Gender (M/F)	103	46/57			
Age at diagnosis (years)	103	1.28	1.30	0.17	5.00
transfusion Rate /year	103	18.57	5.77	6.00	45.00
Height (cm)	103	137.52	17.13	90.00	165.00
Weight (kg)	103	33.47	12.13	13.30	75.50
BMI kg/m^2	103	17.50	4.81	9.96	38.52
Serum ferritin	103	4623.20	304.42	488.00	12000.00

n: Number of cases; SD: standard deviation

On Assessment of BMI on those thalassemic patients, majority of patients (67.96%) were underweight, while only 26 (26.21%) were normal, the remainder were above normal, as shown in table 2.

Table 2.

Classification of all thalassemic patients according to BMI

BMI	No. of patients (103)	Percent
Underweight (<18.5)	70	67.96%
Normal (18.5-24.9)	27	26.21%
Overweight (25-29.9)	3	2.91%
Obesity > 29.9	3	2.91%

On assessment of serum ferritin in all thalassemic patients, we found that 71(68.93%) had Serum ferritin > 2500 ng/ml, 27(26.21%) was between 1000-2500 ng/ml, and only 5 (4.85%) were <1000 ng/ml.

Table 3.

Classification of all thalassemic patients according to S.ferritin level

S. ferritin	No. of patients	Percentage
< 1000	5	4.85 %
1000- 2500	27	26.21 %
>2500	71	68.93 %

Table 4.

The correlation between BMI and S. ferritin level in all thalassemia patients

S. ferritin level	BMI				p-value
	Low	Normal	Overweight	Obesity	
<1000	2	3	0	0	
1000-2500	16	9	1	1	
>2500	52	15	2	2	0.546

Serum ferritin was significantly higher in patients treated with desferal than patients treated with exjade (P<0.001). There was a significant difference in mean age and height of patients on desferal and those on exjade, however there was no significant difference in gender distribution. Age at time of diagnosis was also not significantly different (P=0.247). The rate of transfusion was significantly greater in the group of patients treated with desferal (P=0.008). No significant difference was reported in mean BMI between the two groups (0.195).

Table 5.

 Characteristics of all thalassemia patients according to type of chelating agent

Characteristic	Patient on desferal (n = 49)	Patient on exjade (n = 54)	P†
Age of patient (years)*	16.59 ±5.63	12.63 ±5.29	<0.001 HS
Gender (M/F) **	25/24	21/33	0.216
Age at diagnosis (years) *	1.12 ±1.12	1.42 ±1.44	0.247 NS
Dose (mg/kg) *	40.20 ±6.92	30.48 ±9.07	-----
transfusion Rate /year *	20.14 ±5.93	17.15 ±5.27	0.008 HS
Height (cm) *	143.82 ±13.60	131.81 ±18.09	<0.001 HS
Weight (kg) *	34.98 ±12.01	32.11 ±12.18	0.233 NS
BMI kg/m^2 *	16.85 ± 5.07	18.09 ± 4.53	0.195 NS
Serum ferritin *	6793.20 ±2927.17	2654.10 ±1344.97	<0.001 HS

*mean ±SD; ** number of cases; † Mann Whitney U test; n: number of cases; HS: Highly significant; S: significant; NS: not significant

There was significant correlation between gender of patients and serum ferritin (r=0.335, P=0.019) in group of patients treated with desferal and also there was significant negative correlation between dose of drug and serum ferritin in patients treated with exjade, i.e. the higher the dose is, the less is the serum ferritin.

Table 6.

 Serum ferritin correlation to other parameters

Correlation		Sex	Age of patient	Age at diagnosis	Dose	transfusion Rate	height	weight	BMI
Desferal group	R	0.335	0.104	0.140	0.269	-0.093	-0.002	0.164	0.203
	P	0.019	0.477	0.338	0.061	0.524	0.991	0.262	0.163
Exjade group	R	0.033	0.020	-0.067	-0.360	0.010	0.221	0.064	-0.206
	P	0.813	0.887	0.633	0.007	0.941	0.108	0.647	0.236

r: Spearman correlation coefficient

Discussion

Thalassemia is considered a common hereditary hematological problem in Asia in which the patient needs a regular blood transfusion [12], to eliminate the effects of anemia with its compensatory bone marrow expansion and to allow normal development and extending survival [13]. In this study on a group of transfusion dependent thalassemia major, we found that 70 patients (67.96 %) were underweight (BMI<18.5) and only 27(26.21%) had normal BMI. This result was higher than reported in EGYPT by Fahim M. Fahim et al were they found that only 43% of their thalassemic patients had BMI below normal [14]. Another study (in Iran) by Hashemi A.MD et al also show that BMI was lower than normal in 18.6% only and normal in 81.4% [15]. When S. ferritin was evaluated, there are 71 patients (68.93%) had a level >2500, and 27 patients (26.21%) had a level between1000- 2500. This result was higher than reported by Amil Kumar *et al*, as there are 43.05% had a S. ferritin >2500, and (44.4 %) had a level between1000- 2500 [16]. These results with the too high S. ferritin and too low BMI may be a reflective of the inadequacy of chelation therapy and the consequence of iron overload on growth retardation. When we compare the

characteristics of all thalassemia patients according to the type of chelating agent, there was no difference in BMI between the two groups, but the rate of transfusion and mean S. ferritn was significantly higher in those on desferal, this is explained by the poor compliance of our patients to this type of chelating therapy. The significant difference in mean age and height between patient on desferal and patient on exjade may be related to the small sample size, larger sample may prohibit this result. There was significant correlation between gender of patients and serum ferritin in group of patients treated with desferal (all female patients involved were complaining from amenorrhea). There was significant negative correlation between dose of drug and serum ferritin in patients treated with exjade, i.e. the higher the dose is, the less is the serum ferritin (hence it reflect the effectiveness of this oral chelating therapy in reducing iron overload).

Conclusion

As growth failure in thalassemic patients is a reflective of many factors (chronic anemia, iron overload with its complications, associated chronic medical disease, associated endocrinopathies), study of iron overload alone is not enough to determine growth failure. Exjade (Deferasirox), is more effective in decreasing iron overload, as compliance of our patients is better with this type of chelating therapy. The dose of chelating therapy and the compliance of our patients is needed to be more evaluated, to improve growth and to get a normal BMI.

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