Growth Retardation among Multi-Transfused Thalassemic Patients in Thalassamia Center in Babylon Governorate

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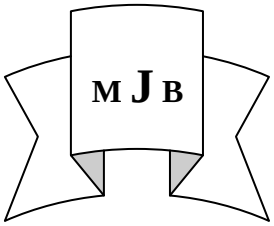

Abstract

Background: Growth retardation can occur as complication of thalassemia as early as the 1st or 2nd year of life but these abnormalities more prominent after the 6 – 8 years of life .

Aims of Study: This study was carried out to determine :

1- rate of growth retardation among thalassemia patients in Babil thalassemia center .

2- the relationship of growth failure with certain variable including age , number of blood transfusion , serum ferritin , mean hemoglobin level, size of spleen , type of thalassemia and gender of the patients .

Patient and Methods: A prospective study was conducted on 110 patient , (67 male , 43 female) with ß- thalassemia , classified as 79 patients with ß- thalassemia major , 23 patient ß – thalassemia intermediate and 8 patients with sickle cell thalassemia , Who were attending the thalassemia center of Babylon maternity and children hospital , from period of march to August 2009 , their age range from one year to 20 years with mean age of 9±2 years.

Control group: One hundred healthy children were taken as control group , their age ranged from 1-15 years, with mean age 7± 2.3years , non of them had history of blood transfusion and they had no family history of hemoglobinopathy .

Result : Thalassemic patients developed 45.5% short stature and 40% weight failure, in comparison to control group (4% short stature , 8% weight failure). Growth retardation was affected by age, increased number of blood transfusion, size of spleen, serum ferritin and hemoglobin level, while there is no difference regarding type of thalassaemia or gender .

Conclusions: Growth is significantly affected by thalassaemia and different factors play a role.

Recommendations: This study emphasized the importance of maintenance of normalized hemoglobin level , good monitoring of growth parameter and iron over load with optimal iron chelation therapy.

الخلاصة

خلفية البحث: ان تاخر النمو يعد احد مضاعفات فقر الدم البحر المتوسط والتي تظهر في السنة الاولى والثانية من عمر المصاب ولكنها تظهر بوضوح بعد السنة السادسة – الثامنة من العمر .

هدف الدراسة

١- ايجاد معدل تاخر النمو بين مرضى فقر الدم البحر المتوسط (الكبير ، المتوسط ، وفقر الدم البحري المنجلي) والذين راجعوا مستشفى بابل التعليمي للنسائية والاطفال مقارنة بالاطفال الاصحاء.

٢- تحديد العلاقة بين تاخر النمو مع بعض عوامل الخطورة (العمر ، تكرار نقل الدم ، مستوى الفرتين في مصل الدم ، معدل الهيموغلوبين ، حجم الطحال ، جنس المريض و نوع الثلاسيميا) .

المرضى وطريقة العمل: دراسة مستقبلية اشتملت على ١١٠ مريضا مصابا بفقر الدم البحري نوع بيتا. (٦٧ ذكر و ٤٣ انثى) ، ٧٩ مريضا مصابا بفقر الدم البحري (النوع الكبير) ، ٢٣ مريضا بفقر الدم البحري (النوع المتوسط) ، وثمان مرضى مصابين بفقر الدم المنجلي البحري ، الذين راجعوا مركز الثلاسيميا في مستشفى بابل التعليمي للنسائية والاطفال للفترة من شهر(اذار لغاية شهر اب ٢٠٠٩) تراوحت اعمارهم من سنة واحدة الى ٢٠ سنة بمعدل عمري (٩ ± ٢) مقارنتها بمئه من الاطفال الاصحاء ، تراوحت اعمارهم بين سنة و ١٥ سنة وبمعدل عمري (٧ ± ٢,٣) سنوات .

النتائج: اظهرت الدراسة ان ٥٠ (٤٥.٥%) مريضا مصابا بقصر القامة و ٤٤ (٤٠%) مريضا مصابا بفشل الوزن. وان عوامل الخطوره لفشل النمو هي العمر وتكرار نقل الدم ، زيادة مستوى الفرتين في مصل الدم ، حجم الطحال و مستوى الهيموغلوبين ، بينما لايتاثر بالجنس ونوع الثلاسميا .

التوصيات: الدراسة توضح اهمية المحافظة على معدل الهيموغلوبين الطبيعي ، وكذلك المتابعة الجيدة لعلامات النمو ، ومتابعة زيادة الفرتين في انسجة الجسم وعلاجها بصورة منتظمة.

Introduction

Normal growth of ß–thalassemia children during 1st 10 years of life depend upon the maintenance of Hb level above 8.5 gm/dl [1], during this period of child , life hypoxia may be the main factor retarding growth and the maintenance of Hb levels above 10-11 gm/dl together with adequate iron chelation therapy makes the ß-thalassemia patients indistinguished from their non thalassemia peers [1].

Growth retardation in thalassemia can occur as early as the 1st or 2nd year of life but these abnormalities are more prominent after the 6-8 years of life [2].

After the age of 10 years despite the fact that adequate level of hemoglobin are maintained, many of the ß- thalassemia children start having decelerate growth[1] .

In pubertal children, there may be a reduced growth spurt with marked deceleration, for which iron over load may be responsible [1].

If desferrioxamin used as iron chelation therapy is used before the age of 3 years, it produces marked stunted growth with a clinical and radiological rickets – like syndrom [1], also desferioxamine is thought to chelate other essential minerals besides iron [1]. or poor growth may associated from higher dose[3].

The hormonal cause of growth retardation in ß- thalassemia children is complex[1].

Besides hypothyroidism and hypogonadism, it has became apparent that growth hormone (GH) also plays a role in their abnormal growth [1] (17 %. has classical growth hormone deficiency [1,4].)Poor growth in thalassemia has associated to several factors like infection , under nutrition , malabsorption of vit D , deficiency of calcium , zinc [5].

Delayed puberty is defined as compete lack of pubertal development in girls by the age of 13 years and in boys by the age of 14 years [6].

Aims of Study

This study was carried out to determine:

1- Rate of growth retardation among thalassemic patients in Babil thalassemia center.

2- The relationship of growth failure with certain variable factors including age, number of blood transfusion, serum ferritin, mean hemoglobin level, size of spleen, type of thalassemia and gender of the patients .

Patients and Methods

I) A prospective study was conducted randomly on 110 patient (67 male and 43
female) with ß- thalassemia, classified as 79 patients with ß- thalassemia major , 23 patient with ß – thalassemia intermediate and 8 patient with sickle cell thalassemia, who were attending the thalassemia center at Babylon maternity and children teaching hospital, from the period of March to August 2009, their age range from one year to 20 years with mean age of 9± 2 years.

They were studied for growth failure and pubertal delay.

II) Control group: of 100 healthy children, their age ranged from one

year to 15 years , with a mean age 7± 2.3 years, non of them had history of blood transfusion and they had no family history of haemoglobinopathies.

III) Detailed history was taken including (name, age, sex, address, family history and examination was obtained for every thalassemic patient and control group including:-

A- Growth parameters were measured for all patients and control group including height , weight and pubertal stage (for teenager only):

1- hight was measured using an age appropriate stadiometer (all measurements were obtained in centimeter and plotted on the centile chart).

Short stature is that height below 3th centile for age and gender based on growth velocity chart [3].

2- weight: was measured by weight scale (all measurement were obtained in kilogram and transformed into centile chart) and the case considered be positive if the weight is below 3 th centile for age and gender .

3- Pubertal assessment was taken according to tanner stage and absence of sign of puberty by the age of 13 years in female and 14 years in male was considered as delay puberty [3].

B- Assessment the size of spleen and classify it according to its enlargement [7].

1-2cm ⟶ just palpable spleen.
3-4cm ⟶ small size spleen.
5-8cm ⟶ big spleen.
> 8cm ⟶ very big spleen.

IV) Blood samples were obtained from all patients and sent for PCV, Hb and serum ferritin .

Statistical analysis [8]**:-**

The statistical analysis was done by using fisher exact test and t- test (by SPSS).

P- value of less than 0.05 is considered to be significant and of less than 0.01 is consider to be highly significant.

Results

Table 1 Growth parameters in thalassemic patients and control group.

	Height		Weight		total
	+ ve cases*	- ve cases*	+ve cases	- ve cases	
Thalassemic patients	50 45.5 %	60 54.5 %	44 40 %	66 60 %	110
Control group	4 4 %	96 96 %	8 8 %	92 92 %	100

There was a highly significant difference of growth retardation (height and weight) among thalassemic patients, in comparison to control group.

p-value < 0.001.

*+ve cases mean bellow 3rd centile

*-ve cases mean above 3rd centile

Table 2 Relation of growth parameters to age in thalassemic patients**.**

Age	Height		Weight		total
	+ ve cases	- ve cases	+ ve cases	- ve cases	
<5 years	5 17.2 %	24 82.8%	5 17.2 %	24 82.8 %	29
≥5-10	11 33.3%	22 66.7%	11 33.3%	22 76.7%	33
≥10-15	16 37.14%	12 42.86%	15 53.5%	13 46.5%	28
≥15 years	18 90%	2 10%	13 65%	7 35%	20
Total	50	60	44	66	110

There was a highly significant difference of growth retardation of both height and weight with increasing age of patients (of more than 10 years).P –value < 0.01.

Table 3 Relation of growth parameters in thalassemic patients to number of blood transfusion.

number of blood transfusion/year .	Height		Weight		total
	+ ve cases	- ve cases	+ ve cases	- ve cases	
<50	17 36.9%	29 63.1%	15 32.6%	31 67.4%	46 100%
≥50-100	18 42.8%	24 57.2%	16 38.09%	26 61.9%	22 100%
≥100	15 68.18%	7 31.82%	13 59%	9 41%	22 100%
Total Pt	50	60	44	66	110

There was a significant increased of short stature with increasing number of blood transfusion (of more than 100 unit). p-value <0.05

There was no significant difference of weight failure with increasing number of blood transfusion. P > 0.05.

Table 4 Relation of growth parameters in thalassemic patients to level of serum ferritin**.**

S. Ferritin	Height		Weight		Total
	+ ve cases	- ve cases	+ ve cases	- ve cases	
<1000	2 13.3%	13 86.7%	3 20%	12 80%	15
≥ 1000-2000	38 48.7%	40 51.3%	33 42.3%	45 57.7%	78
≥2000	10 58.8%	7 41.18%	8 47%	9 53%	17
Total	50	60	44	66	110

There was a significant difference of short stature with increasing level of serum Ferritin (of more than 1000 microgram / litter). P <0.05 .

There was no significant difference of weight failure with increasing level of Ferritin. P > 0.05.

Table 5 Relation of growth parameters in thalassemic patients to mean Hb- level..

Mean Hb level	Height		Weight		Total
	+ ve cases	- ve cases	+ ve cases	- ve cases	
<7	36 55.3%	29 44.6%	33 50.7%	32 49.3%	65
≥ 7-9	10 43.4%	13 56.6%	8 34.7%	15 65.3%	23
≥9	4 18.1%	18 81.9%	3 13.6%	19 86.4%	22
Total	50	60	44	66	110

There was a highly significant difference of growth retardation with decreasing mean hemoglobin level of (bellow 9 gm/dl) . P- value < 0.001.

Table 6 Relation of growth parameters in thalassemic patients to size of spleen.

Size of spleen	Height		Weight		Total
	+ ve cases	- ve cases	+ ve cases	- ve cases	
≤5 just palpable or small size	9 28.1%	23 71.9%	7 21.8%	25 78.2%	32 100%
≥ 5-<8 big spleen	13 34.2%	25 65.8%	16 42.1%	22 57.9%	38 100%
≥8 very big	25 71.4%	10 28.6%	19 54.2%	16 45.8%	35 100%
Splenectomy	3 60%	2 40%	2 40%	3 60%	5 100%
Total	50	60	44	66	110

There was a significant difference of short stature with increased size of spleen .P - value <0.05 .

There was no significant difference of weight failure with increased size of spleen .P- value > 0.05.

Table 7 Relation of growth parameters in thalassemic patients to type of thalassemia.

thalassemic patients	Height		Weight		Total
	+ ve cases	- ve cases	+ ve cases	- ve cases	
ß- thalassemia major	42 53.16%	37 46.84%	33 41.7%	46 58.3%	79
ß- thalassemia intermedia	5 21.7%	18 78.3%	7 30.4%	16 69.6%	23
sickle thalassemia	3 37.5%	5 62.5%	4 50%	4 50%	8
Total	50	60	44	66	110

There was no significant difference of growth failure among different types of thalassemia. P- value > 0.05 .

Table 8 Relation of growth parameters in thalassemic patients to gender of patients**.**

Gender	Height	Weight	Total
	+ ve cases	+ ve cases	
Male	30 44.7%	26 38.8%	67
Female	20 46.5%	18 41.8%	43
Total	50 45.5%	44 40%	110

There was no significant difference of growth retardation with gender of patients. P –value > 0.05.

Table 9-Relation of thalassemic patients with delay puberty according to gender and type of thalassemia**.**

Patients	Delayed puberty	Total	P- value
Gender Male Female	 17 (85%) 8 (80%)	 20 10	>0.05
Thalassemic type Major Intermedia S.thalass	 13 (86.6%) 11 (84.6%) 1 (50 %)	 15 13 2	>0.05
Total patients of thalassemia	25 (83.3%)	30	P< 0.001
Control group	1 (5%)	20	

There was no significant difference of delayed puberty with gender of patients. P >0.05.

There was no significant difference of delayed puberty among different types of thalassemia. P > 0.05.

There was a highly significant difference of thalassemia and delayed puberty in comparison to controls group. P<0.001.

Discussion

The results of our study showed that thalassemic patients developed 45.5% short stature and 40% weight failure, in comparison to control group (4% short stature and 8% weight failure).

Our results are similar to other studies done in other areas of world [4,9, 10].

This indicate that thalassemic patient have a risk factors for growth failure as result from direct relation to iron toxicity especially endocrine gland[11],Intensive chelation therapy especially below 10 years of age [11] or may result form other factors like anemia [5,12] ,hypersplenism and Folate deficiency [12], Calcium and zinc deficiency[5].

Our result is lower than that the results done in other areas of world 62% [12], 60%[13] and 57.7% [14].

This could be explained by patients age included in this study, where most of our patients (62/110) under age of 10 years while other studies were commonly done on patients above the age of 10 years.

Growth failure for both (height and weight) is increased with increasing age of patients due to increased factors affecting growth with aging like iron over load, desferioxamine toxicity, chronic uncorrected anemia [6], under nutrition, zinc deficiency and endocrine complication which increased with aging of thalassemia patients like hypothyroidisms [6].

These result compatible to other studies done in other areas of world like Hong Kong [15], India [16].

Our results are affected by increased number of blood transfusion and level of serum ferritin, which were considered statistically significant for short stature and non for weight failure, however the percentage is increased with number of blood transfusion of more than 100 unit and level of serum ferritin of more than 1000 microgram /liter and these results are compatible to other studies done in India [11], Tehran [12] and Malysia [14].

The patient who transfused 100-200 ml of packed red blood cell/kg/ year getting 116-232 mg/kg/year of iron, thus with regular blood transfusion, iron store increased to many times above normal unless chelation therapy is given leading to free hydroxyl radical [17] ,thus uncontrolled serum ferritin causing endocrine problem by damage of hypothalamus pituitary axis, resulting in growth failure and lack of pubertal spurt[11].

This study shows that growth failure associated with decreasing hemoglobin of below 9 gm/dl implicating chronic hypoxia as a cause [2].

Growth failure is associated with increasing size of spleen which is statistically significant for height but not for weight (however, the percentage of weight failure is increased with increasing size of spleen).

Normally, the spleen is filter for the blood, it removes old normal and abnormal red blood cell. In thalassemia ,most of red cell are abnormal, they often stuck in the spleen and this is why the spleen enlarges and become bigger and bigger and destroying more and more red cells until almost all the blood you transfused just goes directly to the spleen and is destroyed [7], resulting in anemia leading to growth failure.

Our study shows that no significant difference among types of thalassemia (although the percentage of short stature occurs more in ß-thalassmia major than other types) as iron over load which produced appears in all types from different factors.

No significant difference was observed with gender of patients as growth retardation depends mainly on hemoglobin level and iron over load.

delayed puberty is seen in 83.3% of thalassaemic patients in comparison to 5% of control group ,as risk factors occur more in thalassmia like chronic un corrected anemia, iron over load [6].

These result is similar to other studies in Labanon [6],but higher than the results in Tehran [12].

This higher results could be explained by improper management resulting from deficiency of iron chelating therapy, un corrected anemia well in comparison to others.

Conclusion

This study has revealed that the rate of short stature , weight failure and delayed puberty among thalassaemic patients was 45.5%, 40% , 83.3% respectively and it is similar to other studies done in other areas of the world. And the rate of growth failure is directly related to the age of patient, number of blood transfusion, serum ferritin, hemoglobin level and size of spleen.

Recommendations

This study emphasized the importance of maintenance of normalized hemoglobin level, good monitoring of growth parameter and iron over load with optimal iron chelation therapy.

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