Growth Pattern and Sexual Maturation Rate in β-Thalassemia Major Patients from Thalassemia Center Erbil

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ABSTRACT:

BACKGROUND:

Thalassemia is genetic disorder in globin chain production, or it refers to a group of blood disease characterized by decrease synthesis of one of two types of poly peptide chain (α or ß) that form a normal adult human hemoglobin molecule (Hb A- α2 ß2) resulting in decrease filling of red cell with hemoglobin and anemia .Growth retardation can occur as a complication of thalassemia as early as the 1st or 2nd year of life but these abnormalities are more prominent after the 6 – 8 years of life .

OBJECTIVE:

The main objective of the present study was to evaluate the relationship of growth failure and sexual maturity rate (SMR) in children with β-thalassemia major in comparison with controls.

MATERIAL AND METHOD :

In this case-control study, the growth parameters (height ,weight ,and sexual maturation) and S.ferritin of 38 patients aged 8-16 years (24 males 14 females) with β-thalassemia major who were attending thalassemia center in Erbil city Iraqi Kurdistan were compared with those of 38 healthy controls of the same age and gender.

RESULTS:

Underweight and short stature were found in 23 (61%), 30(79%) of patient group and 3(8%), 3(8%) of control group, the mean age of menarche for female patients was 12.31±2.3 and for control female 11.12±1.31years, The SMR were delayed in 37(97.5%) of patients and in 2 (5.5%) of controls. the level of serum ferritin had no significant relationship with delayed SMR.

CONCLUSION:

Growth failure (underweight and short stature) and delay SMR significantly occur in thalassemia patients compared to controls, and such growth retardation was more likely to occur after 10 years of duration of the disease.

KEY WORDS: thalassemia, growth retardation, s.ferritin .

INTRODUCTION:

The thalassemias are inherited disorders of Hemoglobin (Hb) synthesis resulting from an alteration in the rate of globin chain production. Mutations in globin genes causes thalassemia. These mutations result in the impaired synthesis of the β globin . A decrease in the rate of production of a certain globin chains (α, β, γ, and δ) impedes Hb synthesis and creates an imbalance with the others, normally produced globin chains. This imbalance is the hallmark of all forms of thalassemias [1-3]. Retarded growth in thalassemic patient is complex and multi-factorial, it include, chronic hypoxia secondary to anemia when pre-transfusion Hb is below 8.5g/l growth hormone insufficiency due to defective hepatic biosynthesis of somatomedin, insulin-like growth factor1 (IGF1) , and sex steroid deficiency. Hypogonadism, Hypothyroidism. Hypoparathyroidism, Low bone mass, and diabetes mellitus[4,5]. Development of secondary sex characteristics in thalassemic children is markedly delayed as compared to their non-thalassemic siblings and to the expected development criteria. Delay in development of

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secondary sex characteristics appears to be secondary to chronic hypoxia and iron overload [6].In thalassemia major, iron overload is the joint outcome of multiple blood transfusions and inappropriately increased iron absorption associated with ineffective erythropoiesis.Threshold values for iron toxicity are a liver iron concentration exceeding 440 mmoles/g dry weight, serum ferritin >2500 ng/mL, DFO urinary iron excretion >20 mg/day, and transferrin saturation >75%. The outpouring of catabolic iron that exceeds the iron-carrying capacity of transferrin results in the emergence of non-transferrin-bound iron. [7]

AIM OF STUDY:

The main objective of this study was to asses' height, weight, sex maturity rating and menarche in patients with thalassemia major.in comparison to a group and find any relationship to serum ferritin

PATIENTS& METHOD:

A cross sectional study was conducted at thalassemia Center in Erbil City -Iraq, The study was conducted over a period of four months from the 1st of march 2010 to the 30th ofJune 2010.

Thirty eight (24 male and 14emale) patients with β -thalassemia major aged 8– 16 year who attended thalassemia Center in Erbil Governorate during the study period were enrolled in this study. Cases of thalassemia intermedia, thalassemia minor and other hemoglobinopathies were excluded from the study. A group of control matched for age and gender were selected from 3 schools chosen by simple random sampling (primary, secondary and preparatory schools) in Erbil city. Before inclusion in the study, thalassemia was ruled out in the control group. A questionnaire was designed by the researcher , Information was collected from parents of the participants via a face-to-face interview and included age, gender, residence, duration of thalassemia, family history , and the age onset of menarche,. Written consent was taken from parents of each child enrolled in this study.

A clinical examination was performed for both patients and controls which included weight measurement using detecto, (France equipment), height measurement using stadiometer (Seca, Germany made). Because no local growth charts are available, the National Center of Health statistics (NCHS) growth curves are used as reference standards. Weight and height measurement were compared with the normal values on children growth chart of NCHS percentile. The growth of patients and controls was calculated by number of SD above or below the standard mean. Student's t-test was used to evaluate observed differences between groups of measurements and P value less than 0.05 was considered indication of statistically significant difference . [8]

Sexual maturation rate was assessed and adopted by Tanner staging, the mean age of menarche was 13.46years [9]. for estimation of serum ferritin Venous blood samples were obtained. Blood sample were collected between 8:30-9:00 a.m., about 5 mL of blood was withdrawn by venipuncture, using plain tubes. After 25-30 minutes, the serum was separated by centrifugation using a HITACHI centrifuge (model O5P-21) at 5000 rpm for 10 minutes, then the samples were freezed and after collection, the samples were analyzed in Rizgary general hospital by minividus machine. Data were entered into Statistical Package for Social science (SPSS) program for Windows version 17. Quantitative variables were summarized by finding mean ± SD. Mann Whitney U test was used to test the difference in the mean between cases and control and p value less than 0.05 regarded indication of statistically significant difference .

RESULTS :

Table-1The age group and gender of the patients and controls are distributed as shown in table 1 which shows 38(100%) in the age of 8-16 years ,male constitute 24 (63%) and female 14 (37%) in both patients and control group.

Table-2Underweight were found in 23/38(61%) of patients and 3(8%) of control with statistically significant difference .

Table-3Short stature were found in 30/38(79%)of patients and 3/38(8%) of controls with statistically significant difference .

Table-4 Sexula maturation rate were delayed in 37 (97.5%) of patients while in 2 (5.5%) of controls and this was statistically of high significance . The age onset of menarche was delayed in 10/14(71%) of female patients in comparison to 1/14 (7%) of control girls with statistically significance difference .

Table-5 The SMR was delayed in 7 patients with s.ferritin in between 2000-5000mg/dl and in 30 patients with s.ferritin more than 5000mg/dl with statistically significant difference.

Table1: Age and gender distribution of the patients and controls.

Age and Gender	Patients No. and %	Controls No. and %
8-16 years	38(100%)	38(100%)
Male	24(63%)	24(63%)
Female	14(37%)	14(37%)

Patients and controls

Table 2: Weight of the Patients and controls

Weight (kg)	Patients No. and %	Controls No. and %	Chi Square P-Value
Less than 5th centile	23(61%)	3(8%)	0.000
5-95th centile	15(39%)	35(92%)	
More than 95th centile	0	0	
Total	38(100%)	38(100%)	

Table 3: Height percentile of the Patients and controls.

Height (cm)	Patients No. and %	Controls No. and %	Chi Square P-Value
Less than 5th centile	30(79%)	3(8%)	0.000
5-95th centile	8(21%)	35(92%)	
More than 95th centile	0	0	
Total	38(100%)	38(100%)	

Table 4 : Distribution of SMR and menarche between patients and controls.

SMR group	Patients No. and %	Controls No. and %	Chi Square P-value
Normal	1(2.5%)	36(94.5%)	0.000
Delayed	37(97.5%)	2(5.5%)	
Total	38(100%)	38(100%)	
Menarche (14 female)			0.001
Normal Menarche	4(29%)	13(93%)	
Delayed Menarche	10(71%)	1(7%)	
Total	14(100%)	14(100%)	

Table 5: Distrebution of SMR and S.ferritin of patient

SMR	S.ferritin (mg/dl)		Chi Square P-value
	2000-5000	>5000	
Normal SMR	1(12.5%)	0	0.4211
Delayed SMR	7(87.5%)	30(100%)	
Total	8	30	38
Normal Menarche	4(80%)	0(0%)	0.001
Delayed Menarche	1(20%)	9(100%)	
Total	5	9	14

DISCUSSION:

Most patients with β-thalassemia major have delayed growth and sexual maturation , the growth retardation can occur as early as the 1st or 2nd year of life, but these abnormalities are more apparent after 10 years [10] .

In the present study the age and gender of the patients and controls are in between 8-16 years , male constitute 24 (63%) and female 14 (37%) .The results of our study show that Underweight were found in 23(61%) of patients and 3of control , (P value= 0.000) ,while Short stature were found in 30(79%)of patients and 3(8%) of controls (P value= 0.000) , both of these parameters were of statistically highly significant , this is in concordance with [10-12],all these studies indicating that thalassemic patient have a risk factors for growth failure as result from direct relation to iron toxicity especially endocrine glands. failureto initiate Intensive chelation therapy especially below 10 years of age or may result from other factors like anemia ' ,hypersplenism and Folate deficiency, Calcium and Zinc deficiency [10,14,15] .

The number of Thalassemic patients with short stature in our study is more than other studies elsewhere as their results where 62% [15], 60% [16] and 57.7% [17] , This could be explained from patients age who included in this study , were most of our patients (30/38)over the 10 years age in reverse to other studies , where commonly done on patient who are under the age of 10 years. In the present study the SMR were delayed in 37(97.5%) of patients while delayed only in 2 (5.5%) of controls of the same age and sex , this was statistically of high significant (P-value=000) ,and some of them present with complete lack of pubescent changes ,this In consistent with [12,13,18,19]studies . also because of lack of proper chelation.

Regarding the menarche, in the present study, the age onset of menarche was delayed in 10(71 %) of patients incompare to 1 (7%) of controls and this was statistically significant (P-value =0.001) ,this is in concordance with another study in which 74% of thalassemic patients have delayed onset of menarche[11] ,

Regarding S.ferritin level and its effect on menarche in the present study, the age onset of menarche was delayed in 1 (20%) of patients with S.ferritin level between 2000-5000mg/dl in compare to 9(100%) of patients whose S.ferritin is more than 5000mg/dl and this was statistically significant (P-value =0.001) , the age onset of menarche was delayed in 10(71 %) of patients incompare to 1 (7%) of controls and this was statistically significant (P-value =0.001) ,this is in concordance with other studies who were concluded thatPatients with transfusion-dependent thalassemia major tend to have abnormal growth and sexual maturation at puberty, presumably as a result of pituitary iron overload[12,20].another study supports our result which they concluded that ,High serum ferritin levels during puberty are a risk factor for hypogonadism, and high serum ferritin levels during the first decade of life predict final short stature.[21]

CONCLUSION:

We concluded that vast majority of β-thalassaemia major patient attending Erbil thalassaemia center had retardation of growth pattern and delayed in sexual maturity,and they had high serum ferritin levels,which may be contributed to frequent transfusion and poor iron chelation program in this center. proper using of chelating agent in transfusion dependant patient can live normally and can reach puberty by maintaining s.ferritin level within normal range .

REFERENCES:

1. Scott J. Thalassemia syndrome. in ;Behraman RE , Kliegman RM editor. Nelson text book of pediatrics ,18th edition , philadelphia , WBS aunders . 2008:2033-37.
2. Weatherall DJ, Clegg JB.Inherited haemoglobin disorders: an increasing global health problem.Bull World Health Organ. 2001;79:704–12.
3. Forget BG. Molecular mechanisms of b thalassemia. In: Steinberg MH, Forget BG, Higgs DR, Nagel RL, editors. Disorders of hemoglobin genetics, pathophysiology, and clinical management.Cambridge: Cambridge University Press; 2001:252–76.
4. Aleem, A., A. Abdul-Kareem, and M.A.-H. M, Hypocalcemia due to hypoparathyroidism in β-thalassemia major patients. Ann Saudi Med., 2000;20: 364-66.
5. M, M.E., A cardiac involvement in Cooley's anemia.. Ann NY Acad Sci, 2002;119:694.
6. Anice G., Aparna B. and Ved P. C. Development of secondary sex characteristics in multitransfusedthalassemic children Indian Journal of Pediatrics 1997; 64:855-59.
7. Dattani MT, Preece MA. Physical growth& development .In: Farfar&Arnells Textbook of Pediatrics, 5th edition; 1998:349-57.

8. Chaim H. Pathogenesis and management of iron toxicity in thalassemia. Cooley's Anemia: Annals of the New York Academy of SciencesVolume 1202, Ninth Symposium. August 2010: 1-9.
9. Jenkins RR. Menstrual problems. In: Behrman RE, Kliegman RM, Jenson HB eds. Nelson Textbook of Pediatrics.17th ed. Philadelphia, WB Saunders.2004:663-67.
10. Anita S. Growth retardation in thalassemia major patients ;int . Jour. Hum . Genetic 2003;3:237-46 .
11. Roth .e ,Pekrum , Bartz , Jarry , and et-al . short stature and Failure of pubertal development in thalassemia major : evidence for hypothalamic Neurosecretory dysfunction of growth hormone secretion and defective pituitary gonadotropin secretion . Euro . J. pediatric : 1997;156:777.
12. Soliman A, Elzalabany M, Armer M, Ansari BM. growth and pubertal development in transfusion dependant children and adolescence with thalassemia major and sickle cell disease . Clin.Endocr .(oxf) . 1995;42:581 -86.
13. Borgna p , De Slefano P, Zonta , Vullo C , De Sanctic , et-al . Growth and sexual maturation in thalassemia major .J .ped .1985;106:150-55 .
14. Malik , Syed , Ahmed N. Compl. in transfusion dependant patient of B – thalassemia major : pak . J. Med .Sci .2009;25:678 -82 .
15. Heshmat Moayeri ,ZohrenOloomi . Prevalence of growth and puberty Failure with respect to growth hormone and gonadotropins secretion in B- thalassemia Major . Original article ; Arch. Iranian med . 2006;9:329 -34.
16. Seema T, M. Kabra, N. Tandon, R. saxena , et-al .clinico hematological profile of thalassemia intermedia patients . int. J. hum Genets. 2003;3:251- 58.
17. Hamidal,Arini MI, Zarina Ac, Zulkifli , Jamal R. Growth velocity in transfusion dependant prepubertal thalassemia patient : results from thalassemia center in Malaysia : southeast Asian J . Trop. Medic. Public health .2008;39:900 -5.
18. Vahida A.,Torabinezhadm H.,AhmadiA.,Farahmandinia Z.,Kani et al . A cross-sectional controlled study of gonadal function and pubertal development in thalassemia major : Medical Jour. of the Islamic Republic of Iran(MJIRI) May 2003;17:5-9.
19. Saka N ,Sukur M. ,Budar R. ,Anak S. ,Neyzi O. et al . Growth and puberty in thalassemia major: Department of Pediatrics, University of Istanbul, Medical Faculty of Istanbul, Turkey. J Pediatr Endocrinol Metab. 1995;8:181-86.
20. Naomi B, Nancy F. Olivieri, Beverley T, David F. Andrews, Melvin H. Freedman, and F. John H. Effect of Age at the Start of Iron Chelation Therapy on Gonadal Function in β-Thalassemia Major N Engl J Med 1990; 323:713-19.
21. Shlomit S, Doron C, Naomi W, Moshe P, Hagit M, Liora K, Rama Z, Isaac Y, Hannah T. Serum ferritin level as a predictor of impaired growth and puberty in thalassemia major patients. European Journal of Haematology ., Issue 2 February 2005;74: 93–100.