Failure of puberty and linear growth in beta-thalassemia major

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ABSTRACT

Thalassemia major is a severe progressive hemolytic anemia and a serious medical problem worldwide. Endocrine dysfunctions are well described in patients with thalassemia major. Data for endocrine complications from developing countries are scant. Endocrine complications in developing countries may be frequent due to suboptimal iron chelation. The aim of this study was to evaluate the prevalence of delayed puberty and growth failure in patients with beta-thalassemia major. We evaluated the growth and sexual development of 146 patients with thalassemia major aged 10-22 years. The following data were recorded in questionnaire, age, sex, height, weight, serum ferritin levels and pubertal staging. Failure of puberty was present in 75.6% of boys and 68.4% of girls aged 12-22 years. Gonadotropin insufficiency was found in most of the patients with lack of puberty. There was a significant difference between the height of patients with pubertal development (153 ± 9.1 cm) and those with delayed puberty (140 ± 9.1), ($p< 0.001$). Short stature was present in 65.7% of patients. Sixty-nine percent of boys and 62.9% of girls were found to be less than 2 SD below the mean for normal height; after the age of 12, the percentage was 78.9% in girls and 83.8% in boys after the age of 14. We conclude that failure of puberty and impaired growth are very common in our thalassemic patients which necessitates newer protocols of treatment, correct blood transfusion and chelation therapy.

Key Words: Beta-thalassemia major, Growth, Puberty.

ÖZET

Beta-talassemi majörde puberte ve gelişmede gecikme

Talassemi majör, dünya çapında sorun olan, önemli progresif bir hemolitik anemidir. Talassemi majörde endokrin bozukluklar iyi tanımlanmıştır. Ancak gelişmekte olan ülkelerde data yetersizdir. Bu ülkelerde suboptimal demir şelasyonu nedeni ile endokrin komplikasyonlar daha sık olabilir. Bu çalışmanın amacı beta-talassemi majörlü hastalarda gecikmiş puberte ve büyümenin gecikmesini araştırmaktır. On-yirmiiki yaş arasında talassemi majörlü 146 hastada büyüme ve cinsel gelişme araştırıldı. Kullanılan formda yaş, cinsiyet, boy, kilo, serum ferritin düzeyleri ve pubertal evre sorgulandı. Oniki-yirmiiki yaş arası erkek çocukların %75.6'sında, kızların ise %68.4'ünde puberte gecikmesi saptandı. Puberte gecikmesi olanlarda gonadotropin yetmezliği ön planda idi. Pubertal gecikme olanların boyları ile (153 ± 9.1), gecikmiş pubertesi olanların boyları (140 ± 9.1) arasında anlamlı fark bulundu ($p< 0.001$). Hastaların %65.7'sinde kısa boy vardı. Oniki yaş üstünde olan erkek çocukla-

rın %69'u ve kızların %62.9'u normal boyun 2 SD altında, 14 yaş üstünde ise bu oranlar %83.8 ve %78.9 idi. Sonuç olarak bizim talassemi olgularımızda puberte gecikmesi ve boy kısalığı çok sık olup, sorunun çözümü için yeni tedavi protokolleri, doğru kan transfüzyonu ve şelasyon tedavisi gereklidir.

Anahtar Kelimeler: Beta-thalassemia majör, büyüme, puberte.

INTRODUCTION

Endocrine dysfunctions are well described in patients with thalassemia major[1-3]. Investigations have documented evidence of hypothalamic-pituitary dysfunction, hypothyroidism, hypoparathyroidism, adrenal insufficiency and pancreatic dysfunction[4-9]. Transfusion related iron overload is the primary therapeutic complication in thalassemia major[1,6]. The use of iron chelating drugs has been shown to delay the development of iron induced damage of cardiac and liver tissue, resulting in improved survival[1,10]. The ability of desferrioxamine to prevent endocrine damage is less clear[1].

Endocrine problems could result from a variety of factors. Most studies suggest that chronic iron over loading secondary to hypertransfusion therapy is the major cause of the observed abnormalities[2,11]. Data regarding the prevalence of endocrine dysfunction in patients with thalassemia major in Iran are lacking. The aim of this study was to evaluate the prevalence of delayed puberty and growth failure in patients with beta-thalassemia major.

MATERIALS and METHODS

One hundred and forty-six patients aged 10-22 years (84 males, 62 females) with beta-thalassemia major were studied at the Pediatric Department of Shiraz University of Medical Sciences. All patients had received blood transfusion from the age of one month to 11 years (mean 23.11 ± 26.94 months) to maintain pretransfusion hemoglobin concentration > 9.5 gm/dL. Subcutaneous desferrioxamine was started in patients over 3 years of age with serum ferritin concentrations greater than 1000 μg/L. At the time of this study patients were using desferrioxamine by pump (40-50 mg/kg/day, 5 nights/week). Age, sex, weight and height was recorded in the patient's chart. Height was measured by a single observer using a stadiometer. Pubertal staging was performed by the same observer and was assessed according to the criteria of Tanner[12].

Lack of pubertal development was indicated by absence of testes enlargment greater than 2.5 cm in the longest diameter in boys and breast development in girls. Serum ferritin concentrations, liver function tests, hepatitis B surface antigen (HBsAg) and antibody against hepatitis C virus (HCV), serum calcium, phosphorus and blood sugar were measured. Serum follicule stimulating hormone (FSH), luteinising hormone (LH) were measured in girls over 12 and boys over 14 years of age who had not reached puberty. Testosterone was measured in boys over 14 years of age who had not reached puberty. Blood samples were taken from patients on a morning at least 2 weeks after the previous transfusion. Plasma hormone concentrations were determined by radioimmunoassay technique. Statistical analyses were carried out using student's t-test, chi-square test and Pearson correlation co-efficient.

RESULTS

A total of 150 thalassemia major patients were studied, out of which 4 patients were excluded because of death. Characteristics of patients are shown in Table 1. The age of patients ranged from 10-22 years (mean 14.4 ± 2.79 years). Eighty-four patients (57.5%) were male and 62 patients (42.5%) were female. The mean age at the start of desferrioxamine was 7.14 ± 4 years. The me-

Table 1. Characteristics of patients with β-thalassemia major

Characteristic		Value	
M		84 (57.5%)	
F		62 (42.5%)	
Age of patients, years (mean ± SD)		10-22 (14.4 ± 2.79)	
Mean age of start desferrioxamine, years (mean ± SD)		7.14 ± 4	
Mean age of start blood transfusion, months (mean ± SD)		23.11 ± 26.94	
Serum ferritin, μg/L (mean ± SD)			
	Whole group	3365 ± 2172	
Delayed puberty		3868 ± 2350	
	Normal puberty	2947 ± 2061	
	Short stature	65.7% (62.9% F, 69% M)	
Failure of puberty		75.6% M, 68.4% F	
Ht SDS, cm (mean ± SD)			
	Whole group	- 3.17 ± 1.61	
M		- 2.81 ± 1.31	
F		- 3.04 ± 1.24	
Patients with puberty		- 2.05 ± 0.95	(p< 0)
Patients without puberty		- 4.32 ± 1.42	
M patient with puberty		- 2.14 ± 0.98	(p< 0.001)
M patient without puberty		- 4.57 ± 1.32	
F patient with puberty		- 2 ± 0.97	(p< 0)
F patient without puberty		- 4.05 ± 1.5	

Ht SDS: Height Standard Deviation Scores, M: Males, F: Females.

an serum ferritin level was 3365 ± 2172 μg/L (range 270-9980 μg/L). The mean age at the start of blood transfusion was 23.11 ± 26.94 months (range 1-132 months). Hepatitis B surface antigen was positive in 4% of patients and antibody against HCV was positive in 21.5% of patients. The mean weight standard deviation scores (SDS) was -2.1 ± 0.84 kg. In 43.8% of the patients, weight was below the third percentile for age. The mean height SDS was -3.17 ± 1.61. The mean height SDS was -2.81 ± 1.31 cm in boys and -3.04 ± 1.24 cm in girls. Short stature was present in 65.7% of patients (height below the 3rd percentile for age), 62.9% of girls and 69% of boys.

The mean height SDS in boys under 14 years was -2.43 ± 1.22 cm while in girls below 12 years it was -2.94 ± 1.56 cm. In girls above 12 years of age and in boys above 14 years, 78.9% and 83.3% were less than 2 SD below mean for normal height respectively. Failure of puberty was present in 75.6% of the boys over the age of 14 years and in 68.4% of girls over the age of 12 years. Thirty-eight girls were over 12 years and 37 boys were over 14 years. Testosterone, was below normal levels in 98% of the boys over 14 years. Spontaneous FSH and LH secretion were prepubertal in 81% and 86% of adolescent patients respectively.

Luteinising hormone level was 1.68 ± 1.35 mIU/mL and FSH was 3.73 ± 2.74 mIU/mL. The mean age at the start of desferrioxamine for boys with delayed puberty was 6.93 ± 4.1 years while it was 5.9 ± 3 years in boys with puberty; in girls it was 8.9 ± 4 and 7.23 ± 4 years respectively. The mean height SDS in boys without puberty and in those with puberty was -4.57 ± 1.32 cm and -2.14 ± 0.98 cm respectively ($p< 0.001$). The mean height SDS in girls with delayed puberty and in those with puberty was -4.05 ± 1.5 cm and -2 ± 0.97 cm respectively ($p< 0.001$). The mean serum ferritin level in patients with delayed puberty was 3868 ± 2350 μg/L while this level was 2947 ± 2061 μg/L in cases with puberty. This difference was not statistically significant ($p= 0.12$). In 15% of patients with delayed puberty, serum ferritin level was below 2500 μg/L and 47.6% of patients with normal puberty had a serum ferritin level above 2500 μg/L. The mean height SDS in patients with delayed puberty was -4.32 ± 1.42 cm as compared to -2.05 ± 0.95 cm in patients with puberty ($p< 0.001$).

DISCUSSION

Delayed puberty was present in 75.6% of boys all of whom were above the age of 14 years and in 68.4% of girls all of whom were above the age of 12 years. Soliman et al reported lack of puberty in 73% of boys and 42% of girls, between the ages of 13 and 21 years, with thalassemia major[13]. In a study by Gulati et al, 10 out of 11 adolescent or young adult thalassemic patients had hypogonadism[8]. Pignatti and colleagues reported the prevalence of lack of puberty in 38% of females and 67% of males aged 12-18 years[14]. Our data indicates that failure of puberty is very common in our thalassemic patients, mainly in subjects who have serum ferritin levels above 2500 μg/L. Low gonadotropin secretion in most of our patients with failure of puberty indicates secondary hypogonadism. Hypogonadism are extremety frequent in patients with thalassemia[15]. Iron overload has for a long time been considered to be the major cause of endocrine abnormalities of thalassemia major and this is supported by histological studies of different endocrine glands[1,7,16]. The precise mechanism whereby iron overload causes tissue damage is not completely understood, though there is evidence of free radical formation and lipid peroxidation resulting in mitochondrial lysosomal damage. Although the prognosis for survival is good for patients with serum ferritin concentrations below 2500 μg/L, 15% of our thalassemic patients had delayed puberty with serum ferritin levels below 2500 μg/L while 47.6% of our patients with normal puberty had serum ferritin levels above 2500 μg/L[17]. It is possible therefore, that there may be other factors responsible for organ damage. These factors include: chronic anemia, increased collagen deposition secondary to increased activity of the iron dependent protocollagen proline hydroxylase enzyme, with subsequent disturbed microcirculation in the pancreas and parathyroids, chronic liver disease secondary to iron overload and viral infections following repeated blood transfusions[7,18,19].

In this study 62.9% of girls and 69% of boys were less than 2 SD below the mean for normal height. In a study by Pekrun, et al, 40.6% of thalassemic patients were short in stature (height below the 3rd percentile)[20]. Soliman, et al reported prevalence of short stature (less than 2 SD) in 49% of thalassemic patients[13]. Growth retardation has been reported as a common complication in transfusion dependent thalassemia[14,21]. Although delay in onset of puberty is a common cause of growth retardation in adolescent thalassemic patients, growth retardation could also be due to iron overload, toxic effects of desferrioxamine, other endocrinopathies, zinc deficiency, malnutrition, malabsorption and insulin like growth factor 1 deficiency[3,14,15,22]. Abnormal body proportions with truncal shortening are commonly seen and could be due to the disease itself, iron toxicity and toxic effect of desferrioxamine[3]. Our patients suffered from poor control

and irregular follow-up. These data confirm the high prevalence of growth retardation and pubertal delay in thalassemic patients. It is suggested that newer protocols of treatment, optimization of transfusion and chelation therapy be implemented so that such complications can be partly or totally prevented.

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