

Original Article

Prevalence of Growth and Puberty Failure with Respect to Growth Hormone and Gonadotropins Secretion in Beta-Thalassemia Major

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Background: Present transfusion protocols have increased the life expectancy of patients with β -thalassemia major, but siderosis is a major clinical complication of the treatment. Short stature and hypogonadism are extremely frequent in patients with thalassemia.

To investigate the influence of age at the onset of blood transfusion, iron chelation therapy, and serum ferritin levels on growth and pubertal development in thalassemic patients, and the prevalence of these endocrine complications with respect to pituitary somatotrophic and gonadotropic functions, this study was designed.

Methods: Clinical data of 158 patients (82 females and 76 males) with thalassemia major, aged 10 – 20 years (mean age: 15.1 ± 4.8 years) were collected from a pediatric hematology clinic in Tehran. Height was measured and stages of puberty were determined by a pediatric endocrinologist. Serum ferritin concentration, liver function tests, serum calcium and phosphorus, blood sugar, free thyroxine (FT4), TSH, FSH, LH, dehydroepiandrosterone sulfate, testosterone (in boys), estradiol (in girls), and insulin-like growth factor I were measured after overnight fasting. In patients with a height more than 2 standard deviation below the mean, the growth hormone stimulation test was considered. Bone age was determined in all patients.

Results: Thalassemic patients in this study showed a high prevalence of short stature (62%) and hypogonadism (69%). We found a low serum level of gonadotropins (FSH and LH) in over 14-year-old patients with impaired puberty, which indicated that hypogonadotropic hypogonadism is responsible for this complication. Results of growth hormone provocative tests and serum insulin-like growth factor I levels in short stature patients showed a reduced growth hormone response in 38% and low insulin-like growth factor I levels in 42% of thalassemic patients. Short stature and hypogonadism were more common in patients with serum ferritin levels above 2000 $\mu\text{g/L}$ and these complications were significantly more frequent in patients who started treatment later than that of the patients who started treatment in the first years of life ($P < 0.001$).

Conclusion: Short stature and hypogonadism are extremely frequent in our patients with thalassemia, but correct blood transfusion and appropriate iron chelation therapy can prevent or limit these complications. These data support the need for vigilant follow-up of patients with thalassemia in order to treat endocrine dysfunction at an appropriate age.

Archives of Iranian Medicine, Volume 9, Number 4, 2006: 329 – 334.

Keywords: Growth • growth hormone • gonadotropins • puberty • thalassemia major

Introduction

The thalassemias are a heterogeneous group of genetic disorders in which the production of one or more globin chains of hemoglobin is suppressed. Depending on the defective chain, several types of thalassemia have been described. The most common types are β -, $\gamma\beta$ -, and α -thalassemia.

Frequent blood transfusion has increased the life expectancy of patients with β -thalassemia

major, but it causes progressive iron overload.^{1, 2} Iron deposits saturate and transferrin in the reticuloendothelial system, then enter the

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Accepted for publication: 5 April 2006

parenchyma, causing important oxidative damage, mostly to the heart, liver, and endocrine glands.^{3,4}

Researchers have documented evidence of hypothalamic-pituitary dysfunction, hypothyroidism, hypoparathyroidism, adrenal insufficiency, and diabetes mellitus in patients with β -thalassemia major.⁵⁻¹¹ The amount of iron deposits has been the principal factor responsible for the clinical complications of the disease.¹²

It is often difficult to differentiate temporary constitutional delay in puberty from permanent hypogonadotropic hypogonadism. No single test clearly distinguishes constitutional delay in puberty from true hypogonadism.

Gonadotropin releasing hormone (GnRH) testing has been studied extensively in pubertal delay, but may not clarify whether an individual will eventually progress in puberty or will have a permanent defect.

The classic pattern of constitutional growth delay is normal birth weight and length. A subtle decrease in growth velocity occurs about second year of life. Thereafter, stature remains below the fifth percentile through childhood. However, growth velocity remains appropriate for the skeletal age.

An increase in serum dehydroepiandrosterone sulfate (DHEAS) concentration at an appropriate age without an increase in the concentration of serum gonadotropins and gonadal steroids at the expected time of gonadarche is said to occur in hypogonadotropic hypogonadism, whereas a delay in both adrenarche and gonadarche occurs in constitutional delay in puberty.^{13,14}

Linear growth is considered to be decreased when a child's height falls more than 2 standard deviation (SD) below the mean height for age and when the patient's linear growth velocity diminishes to less than 4cm/year or when a child's growth pattern clearly deviates from that of parents. In these cases the child is small for mid-parental size.

Lack of pubertal development is diagnosed when testicles do not enlarge greater than 2.5 cm in the longest diameter in boys older than 14 years, or breasts do not develop in girls older than 13 years.

To date few studies focusing on the prevalence of short stature and failure of puberty with respect to growth hormone (GH) and gonadotropins (FSH and LH) secretion in patients with β -thalassemia major have been conducted in Iran.

We conducted this study among a group of thalassemic patients in Tehran to evaluate the

influence of age at the onset of blood transfusion, iron chelation therapy, and serum ferritin levels on growth and pubertal development, and the prevalence of these endocrine complications with respect to pituitary somatotropic and gonadotropic functions.

Patients and Methods

We collected the clinical information of 158 patients (82 females and 76 males) with β -thalassemia major who referred to the Pediatric Hematology Clinics of Tehran University of Medical Sciences and filled the questionnaires. The patients aged between 10 – 20 years (mean: 15.1 ± 4.8 years), and all were residents of Tehran. We followed up the patients for at least one year in the Pediatric Endocrine Clinic for estimation of growth rate and pubertal status. The mean height SD values were -2.9 ± 1.1 cm in females and -3.2 ± 1.2 cm in male patients.

Medical treatment

In all patients blood transfusion had been started from infancy up to the 6th year of life (mean of 2.5 ± 1.8 years), to maintain the posttransfusion hemoglobin level above 9 – 9.5 g/dL.

Chelation therapy with desferoxamine (DFX) had been started in patients over 2.5-year-old (mean age of 5.8 ± 1.8 years), with serum ferritin concentrations greater than 1000 $\mu\text{g/L}$. The dose of DFX had been 30 – 50 mg/kg/day subcutaneously, 5 – 6 nights a week. The mean serum ferritin level in the studied patients was 3200 ± 1610 $\mu\text{g/L}$.

In boys aged 14 or older who showed no signs of puberty, a course of testosterone enanthate (100 mg intramuscularly every 4 weeks) for 4 – 6 months, and in girls aged 13 or older, a course of ethinylestradiol (5 $\mu\text{g/day}$ orally) for 3 – 4 months was used to initiate maturation of the secondary sexual characteristics.¹⁴

Methods

We collected the data about the age, sex, birth length, parental heights, the age of the puberty for each parent, and the age the blood transfusion and iron chelation therapy was started. All data were processed by the same supervisor.

Height was measured using an age-appropriate stadiometer. All measurements were obtained in cm and transformed into standard deviation scores

(SDS)¹, according to the Tanner and Whitehouse guideline.¹³

Because genetic factors are very important determinants of growth and height potential, it is always worthwhile to compare patients' stature with that of the siblings and parents.^{14, 15} So the measured parental heights were used to calculate Target Height (TH) for each patient as follow:

- For males: (father's height + mother's height)/2 + 6.5 cm;
- For females: (father's height + mother's height) /2 – 6.5 cm.

Stages of puberty were determined according to the classification of Marshall and Tanner.

Serum analysis

We drew a blood sample between 7 and 9 AM from all the participants after 12 – 14 hr of overnight fasting. We then requested serum ferritin concentration, liver function tests, serum calcium and phosphorus, T4, TSH, Insulin-like growth factor I (IGF-I), and blood sugar. Serum DHEAS, testosterone (in boys), estradiol (in girls), FSH, and LH were also measured in girls over 13 years and in boys over 14 years. We determined bone age in all patients as well.

After excluding constitutional growth delay in euthyroid patients who had pathologic short stature (height more than 3SD below the mean) or a slow growth rate (< 4 cm/year), two provocative GH tests (L-dopa; 10 – 30 kg: 250 mg, >30 kg: 500 mg; clonidine; 0.15 mg/m² insulin; 0.05 – 0.1 unit/kg) were performed and samples were taken 0, 30, 60, and 90 minutes after applying the stimulus.¹⁶

In patients with a bone age greater than 10 year the GH provocative tests were performed after sex steroid priming (ethinylestradiol 10 µg once daily orally for 3 days in girls and testosterone enanthate 100 mg in 72 hr before the test in boys).¹⁶

GH deficiency was considered whenever a patient had a severely short stature (height more than 3SD below the mean), a subnormal growth rate, or delayed bone age. The diagnosis was confirmed when the peak GH concentration failed

to reach 10 ng/mL after two consecutive provocative GH tests.

Hypogonadotropic hypogonadism was considered if a boy greater than 14 years, or a girl greater than 13 years had one of the following criteria:

1) he/she was in stage I according to Marshall and Tanner classification,

2) his/her growth velocity was not appropriate for the skeletal age,

3) had an increase in serum DHEAS (normal adrenarache) with low serum FSH, LH, and gonadal steroids (delayed gonadarche), and

4) if during the 3 to 6 months after discontinuing gonadal steroid therapy (maximum of two courses), spontaneous puberty does not ensue, or the concentrations of plasma gonadotropins and plasma testosterone in boys or plasma estradiol in girls do not increase towards pubertal values.

Ethical consideration

This study was conducted in accordance with the guidelines described for thalassemic patients and informed consent was obtained in all cases. The study was approved by the Ethical Committee of Thalassemia Research Center of Tehran University of Medical Sciences, Tehran, Iran.

Statistical analysis

All results were presented as the mean ± SD. We compared variables using Student's *t* test, and Chi-square test. *P* < 0.05 was considered as statistically significant.

Results

Short stature was detected in 98 patients (62%) with thalassemia major (48 [59%] females and 50 [65%] males). Of the 98 patients, 78 were at least 3SD below the mean height (Table1).

At final evaluation, 54 females and 46 males were over 14 years. Of them, 62 patients (69%) showed failure of puberty (33 males [73.2%] and 29 [64.8%] females). As shown in Table 2, the mean height SDS in females with delayed puberty was -3.81 ± 1.28 cm, compared to -2.1 ± 0.82 cm in patients with a normal puberty. The mean height SDS in males with delayed puberty was -4.1 ± 1.58 cm, compared to -2.4 ± 0.69 cm in patients with a normal puberty (*P* < 0.001).

The mean serum stimulated GH was 5.8 ± 3.6

$$^1 \text{ SDS} = \frac{X - Y}{SD}$$

X= patient's height

Y= mean height for normal children at this age and sex

SD= standard deviation of height for normal children at this age and sex

Table 1. Characteristics by gender for short children (all data are presented as mean \pm one standard deviation).

Characteristics	Male (n = 50)	Female (n = 48)
Age	14.3 \pm 1.6	13.4 \pm 2.2
Bone age	10.9 \pm 2.8	11.1 \pm 3.1
Height SDS	-3.8 \pm 2.1	-3.2 \pm 2.6
Growth rate	3.1 \pm 1.4	2.7 \pm 1.5
Maximum stimulated GH (ng/mL)	5.8 \pm 3.6	5.3 \pm 3.4

SDS = standard deviation score.

ng/mL and 5.3 \pm 3.4 ng/mL in male and female patients, respectively (Table 1).

Of the 98 patients with short stature, low levels of IGF-I was detected in 41(42%) and the peak GH response to stimulation test failed to reach 10 ng/mL in 37 (38%) of them.

The mean serum FSH and LH levels in patients with puberty failure were 3.2 \pm 2.2 mIU/mL and 2.1 \pm 1.45 mIU/mL, respectively.

In the present study, 16 patients (10.1%) with diabetes mellitus, 12 patients (7.6%) with hypoparathyroidism, and 7 patients (4.4%) with primary hypothyroidism were diagnosed.

Characteristics of the patients with respect to

Table 2. Height SDS* in the studied thalassemic patients with respect to gender.

	Height SDS	
	Female	Male
Normal puberty	-2.1 \pm 0.82	-2.4 \pm 0.69
Impaired puberty	-3.81 \pm 1.28**	-4.1 \pm 1.58**
P value	< 0.001	< 0.001

* = standard deviation score; ** = all data are presented as mean \pm SD.

the age at the start of blood transfusion, iron chelation therapy, and serum ferritin levels are shown in Table 3.

Discussion

Endocrine dysfunctions have been well described in patients with thalassemia major.^{4-12, 17}

Results of this study show a high prevalence of short stature (62%) and failure of puberty (69%) in a sample of thalassemic patients in Tehran. Hypogonadism is the most common endocrine complication in thalassemia.^{18,19} A large multicentric study in Italy conducted on 1861 patients with thalassemia reported hypogonadism in 47% of females and 51% of males over 15 years old.²⁰

Soliman et al reported the lack of puberty in 73% of males and 42% of females, between the age of 13 – 21 years with thalassemia.²¹ Borgna-Pignatti and colleagues reported puberty failure in 38% of females and 67% of males aged 12 – 18 years.²² In the present study, 73.2% of males and 64.8% of females over 14-year-old with thalassemia had hypogonadism. We found a low serum FSH and LH in most of our patients with impaired puberty, showing that hypogonadotropic hypogonadism secondary to siderosis is responsible for this complication. This finding was similar to the multicentric study in Italy.²⁰

Short stature has been reported as a common complication in transfusion-dependent thala-

ssemia.²² Many factors are involved in the growth retardation of patients with thalassemia. The main ones were chronic anemia, iron overload, hypersplenism, folate deficiency, endocrine disorders secondary to iron overload (hypogonadism, hypothyroidism), and bone dysplasia secondary to DFX toxicity.^{8, 17, 23} GH secretion is also operative. Studies on GH secretion in patients with thalassemia have shown both normal and reduced GH response to stimulation tests, and reduced spontaneous secretion (neurosecretory dysfunction).^{6, 24-29}

Low levels of IGF-I, with normal GH secretion, have also been reported.^{30, 33}

Treatment with recombinant human growth hormone (rhGH) in thalassemic patients with GH deficiency/insufficiency is associated with variable

Table 3. Characteristics of the patients with respect to the onset of treatment and ferritin level.

	Normal puberty	Impaired puberty	P value
Age at the start of transfusion (yr)	1.8 \pm 1.2	4.1 \pm 1.8	0.008
Age at the start of chelation therapy (yr)	4.5 \pm 1.5	7.4 \pm 2.1	0.003
Serum ferritin (μ g/L)	2300 \pm 1900	4100 \pm 2325	< 0.001

clinical response.^{3, 15} Both Soliman et al and Borgna-Pignatti et al reported short stature in 49% and 40.6% of the patients with thalassemia, respectively.^{21, 22}

In this study, 62% of thalassemic patients (65% of males and 59% of females) were less than 2SD below the mean for normal height, but severe short stature (less than 3SD below the mean) was detected in 49% of them. In this study, results of GH simulation tests and serum IGF-I level showed a reduced GH response to two provocative tests and low serum levels of IGF-1 according to sex and age in 38% and 42% of thalassemic patients, respectively. Gulati et al and Theodoridis et al reported a reduced GH response to provocative tests in 51% and 20% of thalassemic patients, respectively.^{9, 34}

Results of this study show that short stature and hypogonadism are very common in our thalassemic patients, mainly in those who have serum ferritin levels above 2000 µg/L and these complications were significantly more common in patients who started treatment later than those who started treatment in the first years of their lives ($P < 0.001$).

Some studies suggest that iron chelation therapy has an important role in gonadic function and growth in patients with thalassemia major and most of the patients who start treatment in the first years of life and have constantly good compliance may show normal growth and sexual maturation.^{17, 18, 20}

In conclusion, in agreement with other reports, our data on a population of patients with thalassemia major indicate that timing of regular blood transfusion and iron chelation therapy influence the growth and puberty in these patients. Better results are achieved in patients treated in the first years of life, suggesting the need for newer protocols for treatment, and optimization of transfusion and chelation therapy in thalassemic patients.

Acknowledgment

The authors wish to thank the residents of Pediatrics Department of Tehran University of Medical Sciences for their cooperation.

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