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ORIGINAL ARTICLE

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Growth hormone (GH) deficiency in patients with β-thalassemia major and the efficacy of recombinant GH treatment

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Abstract Patients with β-thalassemia major still suffer growth retardation. After excluding patients with cortisol deficiency, hypothyroidism, hypogonadism, delayed puberty, malnutrition, severe congestive heart failure, and severely impaired liver function, 29 patients were enrolled in this study. Fifteen (52%) patients exhibited growth retardation and underwent two growth hormone (GH) provocation tests. Eight (53%) of the 15 patients had GH deficiency and were subsequently treated with subcutaneous recombinant human GH (Genotropin, Pharmacia Corporation, Sweden). Growth velocity increased from the pretreatment rate of 3.1±0.4 cm/year to 7.1±1.6 cm/yr ($p<0.001$) after 1 year and to 6.8±1.3 cm/year ($p<0.001$) after 2 years. Patients with growth retardation had lower insulin like growth factor-1 ($p=0.001$) and insulin like growth factor binding protein-3 ($p=0.003$) levels than those without growth retardation. In patients with β-thalassemia major, growth retardation is a common complication and GH deficiency plays an important role. Thalassemic patients with GH deficiency can safely increase their growth velocity with recombinant human GH for2 years; however, the effect on final height still needs to be determined.

Keywords β-thalassemia major · Growth hormone (GH) deficiency · Recombinant human GH

Introduction

The inherited hematological condition β-thalassemia major is not uncommon in Taiwan. Recent medical advances have improved the survival rate of thalassemic patients [1], but endocrine disturbances, specifically growth retardation, are a common problem for sufferers. Many factors have been proposed as causes of growth retardation—the disease itself, the toxic effects of desferrioxamine [2, 3], iron toxicity, malnutrition [4, 5], and endocrine dysfunction—but the mechanisms responsible for growth retardation in these patients have not yet been fully elucidated.

As far as endocrine dysfunction is concerned, apart from thyroid function and the gonads [6, 7], the Growth Hormone (GH)-Insulin Like Growth Factor (IGF)-Insulin Like Growth Factor Binding Protein (IGFBP) axis is believed to play an important role in growth retardation [8, 9]. Both normal and subnormal GH responses to provocation stimulation tests have been previously reported [10, 11, 12, 13, 14, 15]. Estimating the circulating concentrations of IGF-1 and IGFBP-3 allows more accurate evaluation of the GH-IGF-IGFBP axis. Recent reports indicate that treatment of patients with β-thalassemia major with recombinant human GH (rhGH) can lead to significant improvements in growth [8, 9, 10, 11, 16, 17, 18, 19].

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Patients and methods

After excluding patients with hypothyroidism, hypogonadism, delayed puberty, malnutrition, severe congestive heart failure, and severe impairment of liver function, 29 patients with β-thalassemia major were enrolled in the study. There were 16 males and 13 females; mean age was 11.2±4.3 years (range: 5.3 to 21.9 years). All received regular transfusions to maintain pre-transfusion hemoglobin levels above 10 g/dl and desferroxamine was subcutaneously administered for iron chelation (duration: 8–12 h; 5 days/week) at a dose of 30–50 mg/kg/day depending on serum ferritin levels.

Patient heights were measured using standard anthropometric techniques with a wall-mounted stadiometer and the height was categorized according to published local curves [20]. Bone age was determined in accordance with the published methods of Greulich and Pyle [21]. Serum IGF-1 and IGFBP-3 levels were measured with an immunoradiometric assay supplied by Diagnostic Systems Laboratories (Webster, Texas, USA), and we defined low serum IGF-1 and IGFBP-3 as a level below the 3rd percentile.

Patients with growth retardation (body height 2 SD below the mean) underwent two separate GH provocation tests using either

Table 1 Parameters compared between thalassemic patients with and without growth retardation

	Growth retardation (n=15)	No growth retardation (n=14)	p value[a]
Gender			
Male (n=16)	9	7	0.59[b]
Female (n=13)	6	7	
Chronologic age (yr)	12.2±2.6	10.0±5.5	0.18
Bone age (yr)	9.8±2.2	8.9±5.2	0.10
Delayed bone age (yr)	2.4±1.4	1.4±1.3	0.02*
Growth velocity (cm/yr)	3.1±0.4	6.3±1.5	0.006*
Serum ferritin (ng/ml)	3791.3±1702.3	3209.5±2206.5	0.43
ALT (U/l)	28.1±11.8	27.6±15.2	0.91

Values are presented as mean±SD.
ALT alanine aminotransferase (normal value: 0–40 U/l), *n* case number
* $p<0.05$
[a] Student's t-test
[b] Chi-square test

Table 2 Serum IGF-1 and IGFBP-3 compared between patients with and without growth retardation

	GR (n=15)	No GR (n=14)	χ^2 statistic	p value
Low IGF-1	13 (86.7%)	1 (7.1%)	18.34	0.001*
Normal IGF-1	2 (13.3%)	13 (92.9%)		
Low IGFBP-3	11 (73.3%)	2 (14.3%)	10.21	0.003*
Normal IGFBP-3	4 (26.7%)	12 (85.7%)		

We defined low serum IGF-1 and IGFBP-3 as a level below the 3rd percentile.
GR growth retardation, *n* case number
*$p<0.05$

clonidine or insulin hypoglycemia on two different days to assess GH response. After oral clonidine administration at a dose of 0.1 mg/m^2, blood samples were collected at 0, 30, 60, 90 and 120 min for GH measurement. Insulin was intravenously administered at a dose of 0.12 unit/kg to induce hypoglycemia. GH was measured at 0, 20, 40, 60, 90 and 120 min after insulin administration. Plasma GH was measured using the aforementioned immunoradiometric assay. In patients with growth retardation, a peak GH level of less than 10 μg/ml on both tests and bone age delays of more than 2 years was indicative of GH deficiency.

Patients with GH deficiency were treated with subcutaneous rhGH (Genotropin, Pharmacia Corporation, Sweden) doses of 0.1 IU/kg/day for 2 years. Anthropometric measurements, blood pressure, fasting blood glucose, and renal function were assessed at entry and then monthly. Compliance was assessed by self-report and the return of used drug vials.

Data are presented as means±standard deviation (SD). The results were analyzed by analysis of variance followed by the Student's *t*-test. The paired *t*-test was used to compare data before and after therapy in the same group. Differences in serum IGF-1 and IGFBP-3 between thalassemic patients with and without growth retardation were analyzed with the Chi-Square tests and Fisher's Exact test. A p value of less than 0.05 was considered significant.

Results

Twelve patients from the group of 41 patients with β-thalassemia major who had regular follow up at our hospital were excluded for the following reasons: three cases were due to delayed puberty, two cases due to hypothyroidism, three cases due to diabetes, two cases due to hypogonadism, and two cases due to severe heart failure. After the exclusion, 29 patients were enrolled. The results of comparisons of gender, chronologic age, bone age, delayed bone age, growth velocity, serum ferritin, and alanine aminotransferase in patients with and without growth retardation are summarized in Table 1. Variables in patients with growth retardation were not significantly different from those without growth retardation except for delayed bone age (2.4±1.4 vs. 1.4±1.3 years, p=0.02) and growth velocity (3.1±0.4 vs. 6.3±1.5 cm/yr, p=0.006).

Table 2 lists serum IGF-1 and IGFBP-3 levels for patients with and without growth retardation. Our study results indicate that the proportion of subjects with low IGF-1 (χ^2=18.34, p=0.001) and IGFBP-3 (χ^2=10.21, p=0.003) in the growth retardation versus the non-growth retardation group were significantly different.

Of the 29 patients, 15 (52%) patients were found to have growth retardation. Among these 15 patients who then received the two GH provocation tests, eight patients (53%) were found to have GH deficiency. Subsequently, these eight patients underwent rhGH therapy. Growth velocity in the rhGH-treated subjects increased from the pretreatment rate of 3.1±0.4 cm/yr to 7.1±1.6 cm/yr (p<0.001) after 1 year and to 6.8±1.3 cm/yr (p<0.001) after 2 years(Table 3). None of the rhGH-treated patients developed hypertension, fasting hyperglycemia, leukemia, pseudotumor cerebri, or renal function impairment.

Discussion

Thanks to medical advances, prolongation of life expectancy in patients with β-thalassaemia major is possible, but quality of life issues become important. Many causes of growth retardation have been proposed, but mechanisms are not yet fully understood. In this study, patients with

Table 3 Height velocity response to rhGH in thalassemic patients with GH deficiency

Pt. no.	Height velocity (cm/year)			Serum ferritin (ng/ml) before rhGH
	Before rhGH	After 1 year rhGH	After 2 years rhGH	
1	3.5	7.5	6.2	2746
2	2.8	7.5	7.1	2044
3	2.7	8.5	8.2	5838
4	3.0	5.5	6.0	5434
5	3.8	10.0	9.2	6363
6	2.5	5.5	6.2	4065
7	2.9	5.4	5.5	2852
8	3.2	6.6	6.2	4021
Mean	3.1	7.1	6.8	4170
SD	0.4	1.6	1.3	1581

cortisol deficiency, hypothyroidism, hypogonadism, delayed puberty, malnutrition, severe congestive heart failure, and severely impaired liver function were excluded, and the hemoglobin level of all subjects was kept above 10 g/dl. Even after excluding patients with the above conditions, 52% of our study subjects were found to have growth retardation.

The GH-IGF-IGFBP axis is now thought to play an important role in growth retardation, but agreement has not been reached regarding the exact GH-IGF-IGFBP axis abnormality responsible. Using classical GH provocation tests, the GH reserve has been reported to be normal, or reduced. Wonke (1998) et al. reported that growth retardation in iron-overloaded patients is the result of GH deficiency in up to 30% of patients [22]. In our study, 15 patients with growth retardation received two separate GH provocation tests, and eight patients (53%) were found to have GH deficiency. This finding tends to confirm that while not the only reason, GH deficiency plays an important role in growth retardation in patients with β-thalassemia major.

Determination of serum IGF-1 and IGFBP-3 levels promises to be of considerable value in the assessment of GH-IGF-IGFBP axis disorders [23, 24]. We found that patients with growth retardation were more likely to have low IGF-1 and IGFBP-3 than those without growth retardation. Therefore, the defective GH-IGF-IGFBP axis in patients with β-thalassemia major is associated with growth retardation [8, 9].

We found some growth-retarded patients with low IGF levels but without GH deficiency in this study. Serum IGF is produced by the liver and is subject to GH regulation. Hepatic injury in IGF biosynthesis has been suggested as one explanation of growth retardation in thalassemic patients [13]. The elevation of ALT results from acute destruction of hepatic cells. Hepatic injury in thalassemic patients mainly results from iron storage and it is not acute. Therefore, although the mean ALT did not elevate in these patient, hepatic injury in patients with β-thalassemia major might be the cause of low IGF levels in growth-retarded patients without GH deficiency.

Treatment using rhGH has been used for short thalassemic patients with a normal GH reserve or with GH deficiency [8, 9, 10, 11] and has been shown to increase growth velocity irrespective of any GH deficiency [16, 17, 18, 19]. Whether the final height of these thalassemic patients increases after rhGH treatment is an interesting issue. The duration of treatment in most previous studies was 1 year. Cavallo et al. reported that the encouraging results described from the first year of rhGH treatment did not persist during the second and third years [19]. However, our study showed that the growth velocity continue to increase in the second year of treatment in thalassemic patients with GH deficiency. No side effects of rhGH therapy were observed during treatment; therefore, rhGH therapy is safe for at least 2 years.

In conclusion, growth retardation is a common problem in patients with β-thalassemia major. When investigating the GH-IGF-IGHBP axis, GH deficiency was found to play an important role. In addition to GH deficiency, we found that serum IGF and IGFBP-3 levels are associated with growth retardation. Treatment with rhGH can safely increase growth velocity for 2 years, but it remains to be elucidated whether long-term administration will affect the final height. We are currently evaluating the effect of long-term rhGH therapy.

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