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THE RESULTS OF LONG-TERM GROWTH HORMONE REPLACEMENT THERAPY IN TURKISH CHILDREN WITH GROWTH HORMONE DEFICIENCY*

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SUMMARY: Yordam N, Kandemir N, Alikaşifoğlu A (Endocrinology Unit, Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey). The results of long-term growth hormone replacement therapy in Turkish children with growth hormone deficiency. Turk J Pediatr 1998; 40: 55-60.

From a total of 118 patients treated for growth hormone deficiency, 37 (23 boys, 14 girls) have reached their final height. Twenty-five patients had isolated growth hormone deficiency (IGHD) and 12 had multiple pituitary hormone deficiency (MPHD). Growth hormone deficiency was diagnosed and treated late in both boys and girls. The mean height standard deviation score (SDS) for chronological age (CA) increased significantly from -4.43 to -1.94 during the therapy. The target height was not achieved in boys or girls nor in MPHD and IGHD groups, although they have reached the third percentile of the normal Turkish population. The height and chronological age of the patients at the start of the treatment correlated significantly with final height in all patients. Therefore, early diagnosis and treatment is important to complete catch-up growth in growth hormone deficient patients. The height prognosis is improved with administration of a recombinant form of human growth hormone (GH) as daily subcutaneous injections with a dose of 0.1 IU/kg, when compared to the earlier studies with pituitary GH. *Key words: growth hormone deficiency, final height, growth hormone treatment.*

A recombinant form of human growth hormone (GH) has been available for replacement therapy in children with growth hormone deficiency for about ten years. Long-term results of the studies have shown the beneficial effect of GH treatment in improving severe growth deficits existing at the onset of therapy. However, previous results were obtained mostly from patients receiving intramuscular injections of pituitary-derived GH three times/week[1-5]. With the introduction of daily subcutaneous injections of recombinant human growth hormone, growth velocity increased significantly with the expectations of a better final outcome[6].

This report is a retrospective analysis of growth data of 37 patients who have reached their final height from a total of 118 patients treated for growth hormone deficiency (GHD).

Material and Methods

A total of 118 patients were diagnosed with growth hormone deficiency and managed in the Pediatric Endocrinology Unit of Hacettepe University between

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the years of 1986 and 1995. Thirty-seven of them who reached their final height were included in this study.

The following criteria were used for the diagnosis of GHD:

1. A growth velocity below the third percentile according to Tanner growth charts[7].
2. A peak serum GH concentration of less than 10 ng/ml during two pharmacological stimulation tests (L-DOPA and insulin stimulation tests). In prepubertal and early pubertal children with a bone age over eight years, one of the growth hormone stimulation tests was repeated after priming with sex steroids. In boys, a depot preparation of testosterone (100 mg/m^2) was used six to eight days prior to the stimulation test and in girls, ethynyl estradiol (50 mg/m^2) was given over a period of three days prior to the stimulation test[8].

Replacement therapy for other trophic hormone deficiencies was started at least three months prior to growth hormone therapy. Height was measured by Harpenden stadiometer and converted to SDSs to allow comparison of data in children, using reference values at different ages[9]:

$$SDS = \frac{X - \bar{X}}{SD}$$

where X = measurement, $\bar{X}$ and SD = the mean and standard deviation, appropriate for age and sex. Bone age was determined according to the method of Greulich and Pyle[10]. Target heights, corrected for sex, were determined with the use of standard equations[11];

boys, 1/2 (maternal + paternal height + 13),
girls, 1/2 (maternal + paternal height - 13).

Patients were treated with recombinant human growth hormone at a dose of 0.1 IU/kg administered as daily subcutaneous injections, seven times/week.

Each patient was followed up every three months, with the usual clinical and laboratory such as height, weight, pubertal stage and total blood count, routine biochemistry and thyroid hormones. Bone age was determined every six months.

Treatment ended when a bone age of at least 14 years (girls) or 16 years (boys) was reached.

Data were analyzed using Statistical Package for Social Sciences for Windows v. 5.01 (SPSS, Inc., USA). Descriptive data are expressed as mean (SD). Means of paired data were compared by Wilcoxon signed rank test. Means of non-paired data were compared by Mann-Whitney U test. Correlations were made with the Spearman rank test. Differences were considered significant at $p < 0.05$.

Results

Table I shows the auxological data of patients before and at the end of the GH therapy. Twenty-five patients had isolated growth hormone deficiency (IGHD) and 12 had multiple pituitary hormone deficiency (MPHD). None of them had an organic cause for GHD. The mean peak GH response during the L-DOPA stimulation test was 4.1 (2.0) ng/ml in the IGHD group and 1.2 (0.8) ng/ml in MPHD group. During the insulin stimulation test it was 2.5 (2.4) ng/ml and 1.5 (1.6) ng/ml, respectively.

Table I: Auxological Data of All Patients and Patients with Isolated Growth Hormone Deficiency (IGHD) and Multiple Pituitary Hormone Deficiency (MPHD) Before and at the End of Therapy

	IGHD (n = 25)	MPHD (n = 12)	All Patients (n = 37)
Chronological age (CA, years)			
Mean (SD)	12.0 (2.3)	11.5 (3.0)[a]	11.85 (2.59)
Bone age (BA, years)			
Mean (SD)	8.5 (2.9)	6.1 (2.3)[b]	7.75 (2.93)
Height SDS for CA			
Mean (SD)	-4.3 (1.2)	-4.6 (1.3)[a]	-4.43 (1.29)
Height SDS for BA			
Mean (SD)	-1.1 (1.4)	0.1 (2.0)[a]	-0.74 (1.75)
Pretreatment height velocity			
cm/year, Mean (SD)	3.3 (1.0)	3.0 (0.6)[a]	3.26 (0.97)
Final height SDS			
Mean (SD)	-2.06 (0.8)	-1.7 (0.4)[a]	-1.94 (0.74)
Target height SDS			
(Mean (SD)	-1.1 (0.7)	-1.01 (0.6)[a]	-1.07 (0.72)
Duration of therapy, months			
Mean (SD)	45.6 (17.1)	56.2 (18.8)[a]	49.6 (18.1)

a: $p > 0.05$.
b: $p < 0.05$.

Growth hormone therapy started late in both boys and girls but significantly later in boys than in girls ($p < 0.05$, Table II). The administration of growth hormone increased growth velocity effectively and the increment was sustained during the therapy (Fig. 1). As a result, the mean height SDS showed a significant increase during the therapy from -4.43 to -1.94. In the MPHD group, the mean bone age was significantly retarded compared to that in the IGHD group, whereas all other auxological parameters were not significantly different at the start of

the treatment. The target height was not achieved in either MPHD or IGHD groups, but the mean difference between final height and target height was similar in both groups.

Table II: Auxological Data of Boys and Girls Who Have Reached Their Final Height

	Boys (n = 23)	Girls (n = 14)
Chronological age (CA, years) Mean (SD)	12.67 (2.38)	10.49 (2.42)[a]
Bone age (BA, years) Mean (SD)	8.24 (2.89)	6.94 (2.88)[b]
Height SDS for CA Mean (SD)	-4.46 (1.30)	-4.38 (1.31)[b]
Height SDS for BA Mean (SD)	-0.43 (1.54)	-1.26 (1.9)[a]
Pretreatment height velocity (cm/year) Mean (SD)	3.36 (1.06)	3.07 (0.80)[b]
Final height, cm Mean (SD)	161.8 (4.5)	149.0 (4.8)
Target height, cm Mean (SD)	168.8 (2.7)	154.3 (7.1)
Final height SDS Mean (SD)	-1.79 (0.6)	-2.10 (0.7)[b]
Target height SDS Mean (SD)	-0.84 (0.4)	1.49 (0.9)[a]
Duration of therapy, months Mean (SD)	48.8 (17.8)	54.3 (19.6)[b]

a: $p < 0.05$. b: $p > 0.05$.

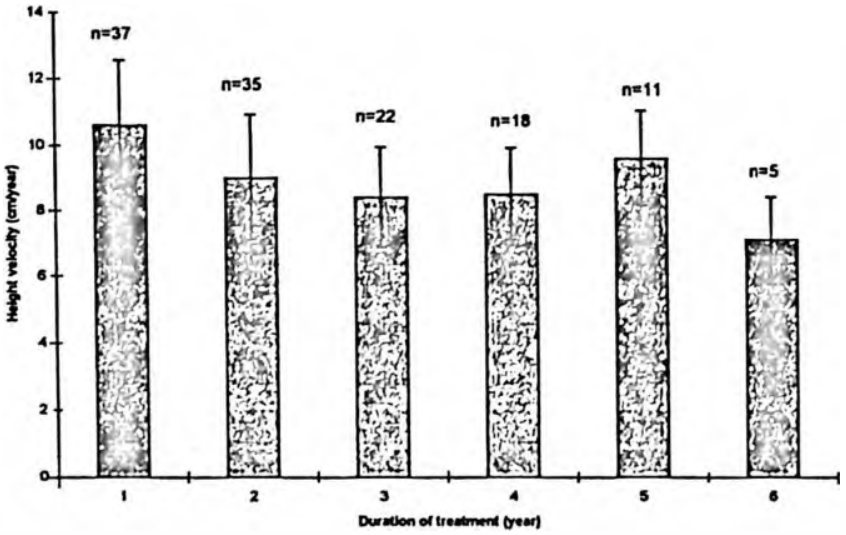

Fig. 1: The mean growth velocity of 37 patients during growth hormone therapy.

No significant difference was found in bone age, height SDS for CA, pretreatment height velocity and duration of therapy between girl and boys (Table II). Target height was not achieved in either sex, although they reached the third percentile of normal Turkish men (162 cm) and women (148.5 cm)[12]. The duration of therapy was not significantly different in either group ($p > 0.05$). The height and chronological age of the patients at the start of the treatment correlated significantly with final height in all patients ($r = 0.44$; $p < 0.05$, $r = 0.47$; $p < 0.05$).

During the therapy, serum T_4 levels decreased in eight patients with isolated growth hormone deficiency; Na-L thyroxin was added to their therapy. In two patients, myalgia and elevated creatine phosphokinase (CPK) levels were observed. The clinical and laboratory investigations suggested myositis in these patients as reported previously[13].

Discussion

Until 1985, human pituitary GH was given three times a week at low doses because only small amounts were available. The results of the studies with pituitary GH showed the failure of this therapy to normalize the final height in growth hormone deficient children[1,2,4,5]. To optimize the replacement therapy, the dose regimen for GH treatment has changed after the production of rhGH in terms of frequency and route of administration. Recently, better final outcomes have reported daily subcutaneous injection of rhGH[14-17].

In this study, a final height SDS of -1.94 was achieved which is similar to the results obtained in other studies. The correlation of final height with height and chronological age at the start of the treatment underlines the importance of early diagnosis and treatment in growth hormone deficiency.

Price and Ranke[18] reported final height in 95 children with idiopathic GH deficiency. Their median final height SDS was -1.03 which is higher than our findings. This is possibly due to earlier diagnosis and treatment and also to the less severe growth retardation of their patients at the start of the treatment (-4.43 vs -2.80).

In our study, the mean final height SDS was slightly higher in the patients with MPHD than in the patients with IGHD, although the difference was not significant. Similar results were obtained by Severi[19], whereas in other studies a better final outcome was reported in the patients with MPHD[1,4]. These controversial results emphasize that there are many different factors affecting final height in growth hormone deficient children.

In conclusion, the overall height gain and final height observed in this study appear promising although target height was not achieved. Analysis of the factors associated with final height may improve the management protocols and consequently a better final outcome could become possible.

REFERENCES

1. Burns EC, Tanner JM, Preece MA, Cameron N. Final height and pubertal development in 55 children with idiopathic growth hormone deficiency, treated for between 2 and 15 years with human growth hormone. Eur J Pediatr 1981; 137: 155-164.
2. Joss E, Zuppinger K, Schwarz HP, Roten H. Final height of patients with pituitary growth failure and changes in growth variables after long-term hormonal therapy. Pediatr Res 1983; 17: 676 679.
3. Bourguignon JP, Vandeweghe M, Vanderschueren-Lodeweyckx M, et al. Pubertal growth and final height in hypopituitary boys: a minor role of bone age at onset of puberty. J Clin Endocrinol Metab 1986; 63: 376-382.
4. Hibi I, Tanaka T. Final height of patients with idiopathic growth hormone deficiency after long-term growth hormone treatment. Committee for Treatment of Growth Hormone Deficient Children, Growth Science Foundation, Japan. Acta Endocrinol (Copenh) 1989; 120: 409-415.
5. Libber SM, Plotnick LP, Johanson AJ, Blizzard RM, Kwiterovich PO, Migeon CJ. Long term follow-up of hypopituitary patients treated with human growth hormone. Medicine 1990; 69: 46-55.
6. Kastrup KW, Christiansen JS, Andersen JK, Orskov H. Increased growth rate following transfer to daily sc administration from three weekly im injections of hGH in growth hormone deficient children. Acta Endocrinol (Copenh) 1983; 104: 148-152.
7. Tanner JM, Davies PS. Clinical longitudinal standards for height and height velocity for Northern American children. J Pediatr 1985; 107: 317-329.
8. Ranke MB, Haber P. Growth hormone stimulation tests. In: Ranke MB (ed). Functional Endocrinologic Diagnostics in Children and Adolescents (1st ed). Mannheim: J & J Verlag 1992: 61-75.
9. Tanner JM, Whitehouse RH, Takaishi M. Standards from birth to maturity for height, weight, height velocity and weight velocity of British children. Arch Dis Child 1965; 41: (Part 1) 457-471; (Part II) 613-635.
10. Greulich WW, Pyle SJ. Radiographic Atlas of Skeletal Development of the Hand and Wrist (2nd ed). California: Stanford University Press; 1959: 1-276.
11. Cowell CT. Short stature. In: Brook CGD (ed). Clinical Pediatric Endocrinology (3rd ed). London: Blackwell Science Inc., 1995; 136-172.
12. Neyzi O, Binyıldız P, Alp H. Growth standards for Turkish children. Heights and weights. Courier 1979; 29: 553-558.
13. Yordam N, Kandemir N, Topaloğlu H, Göğüş S, Küçükali T. Myositis associated with growth hormone therapy. J Pediatr 1994; 125: 671.
14. Bramswig JH, Schlösser H, Kiese K. Final height in children with growth hormone deficiency. Horm Res 1995; 43: 126-128.
15. Chipman JJ, Hicks JR, Holcombe JH, Draper MW. Approaching final height in children treated for growth hormone deficiency. Horm Res 1995; 43: 129-131.
16. Frisch H, Brinbacher R. Final height and pubertal development in children with growth hormone deficiency after long-term treatment. Horm Res 1995; 43: 132-134.
17. Rikken B, Massa GG, Wit JM. Final height in a large cohort of Dutch patients with growth hormone deficiency treated with growth hormone. Dutch Growth Hormone Working Group. Horm Res 1995; 43: 135-137.
18. Price DA, Ranke BM. Final height following growth hormone treatment. In: Ranke MB, Gunnarsson R (eds). Progress in Growth Hormone Therapy, 5 years of KIGS (1st ed). Mannheim: J & J Verlag 1994: 129-144.
19. Severi F. Final height in children with growth hormone deficiency. Horm Res 1995; 43: 138-140.