

Response of Growth and IGF-I to the Growth Hormone Therapy on the Pituitary Dwarfs

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Purpose: This study was made to assess the response of growth to the growth hormone with the velocity and scores of height growth, to compare these findings with familial short stature and to examine the correlation between the IGF-I reaction and the dose of growth hormone, height velocity and scores.

Methods: The study group consisted of 9 patients with pituitary dwarfism who were followed up between 1986 and 1996 periods and given growth hormone treatment. Serum growth hormone and insuline-like growth factor-I were measured by using immunoradiometric method (IRMA-GH-DSL and IRMA-IGF-I-DSL kits). The results were compared with 9 familial short stature and 9 healthy controls.

Results: The patients with growth hormone deficiency got benefit of growth hormone therapy, and the levels of height, height SDS, height velocity and height velocity SDS were increased. The height SDS levels according to familial short stature and control groups were found lower and in correspondence to this the height losses were found high. Correlation was found between the serum IGF-I levels and pubertal periods when the three groups (pituitary dwarfism, familial short stature and control) were evaluated together. Correlation was not found between the basic and stimulated growth hormone levels and isochronal serum IGF-I levels which were recorded after quitting the therapy for one month. Relation was not recorded between the total GH dose given by higher and daily injections for 4 days and the serum IGF-I levels which were recorded on the fourth day, too. But it was observed that these IGF-I levels increased significant degrees according to the basic and stimulated measure of serum IGF-I levels.

Conclusion: In this study it was shown that the values of height, height SDS, height velocity and height velocity SDS belonging to the cases of growth hormone deficiency had significantly increased and the levels of IGF-I had increased as a response to the therapy. Ann Med Sci 2000;9:96-101

Key words: Growth hormone deficiency, growth hormone therapy, IGF-I

The response of growth to the therapy of biosynthetic growth hormone (GH) on the pituitary dwarfs has been described since 1986^{1,2,3,4,5}. The dose of GH, the frequency of practice during the week and the early start to therapy were shown as the elements which increased the affect of growth hormone on growth^{6,7,8,9,10}. It is reported that the fastest response to the growth hormone

therapy was in the first year of the cure.

The levels of serum insuline like growth factor-I (IGF-I) which was found low in the deficiency of growth hormone also increase by the therapy of GH^{11,12}.

This study was made to value the response of growth to the growth hormone with the velocity and scores of height growth, to compare these findings with familial short stature and to examine the correlation between the IGF-I reaction and the dose of growth hormone, height velocity and scores.

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Patients and Methods

This study was made on a total of 9 patients with pituitary dwarfism who were followed up between 1986 and 1996 periods and take GH treatment, and 9 children with familial short stature and 9 healthy children. 7 of 9 pituitary dwarfs were boys, two were girls and all of them were prepubertal. 7 of 9 familial short stature were boys and two were girls, their pubertal stage were 1-P IV, 1-P III, 3-P II, 4-P I. 7 of 9 healthy children were boys, two were girls and their pubertal stage were 2-P III, 1-P II, 6-P I. Bone age was estimated by Greulich-Pyle¹³ method. We computed height SDS and height velocity with using Tanner standards^{14,15}. Growth hormone stimulation tests were made by insulin and L-Dopa.

We measured serum GH and insuline-like-growth-factor I (IGF-I) levels by using immunoradiometric method (IRMA-GH-DSL and IRMA-IGF-1 DSL kits).

It was conducted with the SPSS-PC 5.01 program. Values were shown as average $\pm$ SD. $P < 0.05$ was considered statistically significant. In analysing non-continuous variables chi-square and where appropriate the Fisher-exact tests were used. In the analysis of continuous variables the Student T-test and Oneway-Anova tests were used. In this comparisons where the case number is not enough the Mann-Whitney-U and Kruskal-Wallis tests were used.

Results

The findings at the beginning of the GH therapy of the pituitary dwarfs group are shown Table-1. Among these patients, 4 had idiopathic GH deficiency, 2 had pituitary hypoplasia and in three, there was GH deficiency due to organic lesion. When mean values for calendar age, bone age, height, height SDS, height velocity and height velocity SDS of the pituitary dwarfs group determined at the beginning of the GH therapy was compared with familial short stature and control group, though calendar age was in harmony, all values were found to be significantly low (Table-2). The significant growth response determined with examination of these parameters after GH therapy is shown table-3-4. The evaluation of the IGF-I response to excess GH dosage and frequency is seen Table-5.

Discussion

In this study it was shown that the values of height, height SDS, height velocity and height

velocity SDS belonging to the cases of growth hormone deficiency had significantly increased and the levels of IGF-I had increased. As a response to the therapy, the values of height velocity such like 6.8 ± 1.8 cm/year¹⁶, 7.1 ± 0.47 cm/year¹, 8.1 ± 1.9 cm/year⁴, 9.22 ± 1.07 cm/year were given¹⁶. It is mentioned that the height velocity had decreased in the second year. Girard and Gourmelen¹ established that the height velocity was 6.7 cm/year in the second year in a research they made on 289 patients with growth hormone deficiency. The height velocity of our cases are established by taking the whole time of observation, not only the first and second years of therapy, the mean annual height velocity had been found 7.63 ± 2.71 cm/year. This value is in accord with the values in literature. In accomodation of our findings the values of height velocity SDS had increased from negative (-3.19 ± 1.76) to positive (3.6 ± 5.23) values. Positive correlation^{6,17,18} is shown between the response of growth in the first and second years of growth hormone therapy and the dose of growth hormone and the frequency of application during the week. In our cases the growth hormone was given as 13.33 ± 4.47 units/week (approximately 12 unite/m²) total dose 2-4 injection, there was no correlation found between this GH dose and height velocity SDS values. On the contrary that it showed an important increase the height SDS value of the patients stayed in negative values (-3.44 ± 1.26) (Table 4). This result show us that our cases have lost height and they will not reach their own height standards. In literature it is reported in the studies on this subject that the loss in height will not be regained with the growth hormone therapy, the new height losses will be prevented and they will be able to reach to the height expected by the growth potential foreseen at the beginning of the therapy whereas the normal standards will not be provided^{6,10}. For this reason it's mentioned that therapy should be started before height loss occurred. The average age of our patients when they started the therapy was 11.70 ± 4.01 .

In order to evaluate the affect of growth hormone therapy better, the height SDS, height velocity and height velocity SDS values of our patients were compared with the height SDS, height velocity and height velocity SDS values of children with familial short stature. The calendar age avarege of pituitary dwarf groups at the beginning of the therapy was in accord with the familial short stature. The bone age, height,

height SDS, height velocity and height velocity SDS values (according to the calendar and bone age) were highly lower than the familial short stature group (in order $p < 0.01$, $p < 0.001$, $p < 0.005$, $p = 0.009$, $p = 0.005$, $p < 0.015$). After GH treatment the final findings of these parameters of the pa-

tients were in accord with the findings of familial short stature group except height SDS values (Table 2,3). There was a significant difference ($p=0.0003$) between the highest growth hormone responses to the GHST applied with insuline.

The pituitary dwarfs' serum IGF-I values measured in the final controls of growth hormone therapy process were found significantly lower than the values of familial short stature and control group ($p=0.003$ and $p=0.002$). It is reported in different studies that there's correlation between serum IGF-I values and calendar age, bone age, gender and pubertal stage^{19,20}. On the contrary that the calendar ages of the patients were statistically unimportant than the familial short stature group, and significantly higher than the control group ($p=0.05$), according to the bone age, gender and pubertal stage, these three groups were in accord with each other (Table-3). Because of this reason it was possible to compare the serum IGF-I values in three groups. When all of the cases (pituitary dwarf, familial short stature and control) were evaluated together, correlation was found between serum IGF-I values and pubertal stages.

In many studies it is shown that the maximum level of serum IGF-I in human life is reached during puberty^{21,22,9,23}. The serum IGF-I values of familial short stature group and control group are close to pubertal values and there is not a significant difference found between them (Table-3). However, IGF-I levels in the patient group receiving GH therapy were found to be close to the prepubertal bottom level. And correlation was not found between the height SDS and height velocity SDS and serum IGF-I values of our patients. In the literature the correlation between the response to the growth hormone therapy and the serum IGF-I levels was searched and the contradictory results were reported. In normal children and growth hormone deficiency significant correlation was shown between the height velocity and IGF-I correlation^{24,25}. Rosenfeld et al²⁶ had reported that there is no correlation between serum IGF-I level and height velocity, autocrine and paracrine affects and local intracellular and local interstitial IGF-I concentration is the affective element on growth. Although Costin et al²² found correlation between serum IGF-I levels and height velocity of pubertal stage short children they could not show it on prepubertal children. Hindmarsh et al.²⁷ could not find either a correlation between the serum IGF-I levels or height velocity of short prepubertal children.

Serum IGF-I levels are known to reflect the GH dependent and changes in GH level. Costin et al.²² found positive correlation between 24 hours average GH concentration and serum IGF-I levels of short children. Sanayama et al²⁸ found positive relation between the spontaneous GH

concentration and plasma IGF-I levels of short children. Correlation was not found between the spontaneous GH levels and isochronal measures of serum IGF-I levels of our patients. Albertson et al¹¹ found the serum IGF-I levels of short cases with low 24 hours spontaneous GH secretion was normal. It was shown that the serum IGF-I concentration in growth hormone deficiency can be found % 7.8 by Ranke et al²⁹ and % 15.8 rate by Dean et al¹². D'Ercole³⁰ reported that serum IGF-I levels are controlled by numerous factors.

In growth hormone deficiency a significant correlation was shown between the highest levels of growth hormone measured by the provocative tests and isochronal measure of serum IGF-I levels²⁴. Correlation was not found between the highest concentration of growth hormone of our patients measured as a response to the stimulation test with made insuline and the serum IGF-I concentration measured during this period.

It's reported in different researches that there's correlation between growth hormone dose and the serum IGF-I levels in growth hormone deficiency and the dose and the frequency of growth hormone affects the serum IGF-I levels^{11,12}. Correlation was not found between the total weekly dose (13.33 ± 4.47 u/H) of growth hormone given to our patients by dividing into 2-4 equal doses and the serum IGF-I levels. After this dose was increased to 14.22 ± 3.52 units and given by 4 equal doses in 4 days, the serum IGF-I levels (144.8 ± 102.2 ng/ml) was found significantly higher than the basic and stimulative measures of serum IGF-I levels (in order $p=0.01$, $p=0.007$). Correlation was not found between this growth hormone dose and IGF-I levels.

As a result, the patients with growth hormone deficiency got benefit of growth hormone therapy, and the levels of height, height SDS, height velocity and height velocity SDS were increased. The height SDS levels according to familial short stature and control groups were found lower and in correspondence to this the height losses were found high, the importance and obligation of early start to therapy was found out once more time. Correlation was found between the serum IGF-I levels and pubertal periods when the three groups (pituitary dwarfs, familial short stature and control) were evaluated together. Correlation was not found between the basic and stimulated GH levels and isochronal serum IGF-I levels which were recorded after quitting the therapy for one month. Relation was not recorded between the total GH dose given by higher for 4 days and daily injections and the serum IGF-I levels which were recorded on the fourth day, too. But it was observed that these serum IGF-I levels increased significant degrees according to the basic and stimulated measure of serum IGF-I levels.

Table 1. The findings of the patients with pituitary dwarfism at the beginning of the GH therapy

CASE	SEX	AGE (year)	BONE AGE (year)	HEIGHT (cm)	HEIGHT SDS	HEIGHT VELOCITY (cm/year)	HEIGHT VELOCITY SDS	Follow up time (year)	GHST peak GHng/ml	RADIOGRAPHY		Diagnosed	Treatment		
							Calendar Age	BoneAge	İnsülin	L-Dopa	CT	MRI			
MT	E	13.00	4.50	125.0	-4.15	3.42	-3.13	-3.83	3.92	1.2	-	N	Pituitary Hypoplasia	Pituitary Hypopla- sia	Na-L-Thyroxine GH Cortisone Testosterone
SG	E	17.25	11.00	132.7	-6.25	3.07	-5.16	-2.76	6.09	1.9	1.54	N	-	IGHD	Na-L-Thyroxine GH
ÖA	E	9.08	4.00	100.4	-5.21	2.80	-3.41	-2.53	1.75	1.31	-	N	N	IGHD (familial)	Na-L-Thyroxine GH Testosterone(3d)
RG	E	17.50	13.00	127.5	-7.05	1.94	-2.52	-5.73	3.09	1.4	-	N	-	IGHD	Na-L-Thyroxine GH Testosterone
HE	E	10.50	5.66	120.0	-2.99	4.00	-1.57	-2.27	1.50	0.1	1	N	Pituitary Hypoplasia	Pituitary Hypopla- sia	Na-L-Thyroxine GH Cortisone Testosterone
CI	K	5.66	3.00	100.6	-1.96	1.56	-4.75	-4.78	1.66	4.4	-	N	Pituitary Mass	Langer- hans Histiosi- tosis GHD	Kemotherapy Radiotherapy Desmopressin Na-L-Thyroxine GH
SB	E	11.41	3.25	114.2	-4.38	0.60	-5.69	-5.46	0.33	1.05	2.12	Pituitary Microade- noma	-	Pituitary Adenoma GHD	Operation DDAVP Na-L-Thyroxine GH Cortisone Testosterone(3d)
TK	K	7.75	3.00	101.8	-3.82	4.32	-2.01	-2.62	5.50	1.65	-	Postop Su- prasellar Calcification Orbital CT: Mass	Postop Su- prasellar Calcification	Eosino- philic Granu- loma GHD	Operation Kemotherapy Desmopressin Na-L-Thyroxine GH
DZ	E	13.16	4.50	116.0	-4.78	5.57	-0.43	-0.97	0.79	2.93	2.4	N	-	IBHY 32 46,XY frag13q ³²	Na-L-Thyroxine GH

Table 2. The comparison of the findings of the patients between pituitary dwarfism and familial short stature and control groups at the beginning of GH therapy

FINDINGS	PITUITARY DWARFISM	FAMILIAL SHORT STATURE	CONTROL	A-B	A-C	B-C
	A	B	C			
AGE (year)	11.70±4.01 (5.66-17.50)	13.38±2.31 (10.16-16.91)	11.28±1.92 (9-14)	p> 0.05	p>0.05	p>0.05
BONE AGE (year)	5.76±3.66 (3.00-13.00)	11.28±2.11 (8.83±15.00)	10.70±1.78 (8-13.5)	p<0.01	p<0.01	p>0.05
HEIGHT (cm)	115.35±12.19 (100.4-132.7)	140.16±8.84 (130-161.4)	145.11±13.67 (125-170)	p<0.001	p<0.001	p>0.05
HEIGHT SDS	-4.51±1.56 (-7.05 / -1.96)	-2.15±1.29 (-5.14 / -1.08)	0.18±1.15 (-0.76 - -2.71)	p=0.005	P=0.0003	p=0.003
HEIGHT VELOCITY (cm/year)	3.03±1.52 (0.60 - 4.32)	5.60±1.64 (3.53 - 8.12)		p=0.009		
HEIGHT VELOCITY SDS (Calendar age)	-3.19±1.76 (-5.69 / -0.43)	0.74±2.63 (-0.23 / -5.10)		p=0.005		
HEIGHT VELOCITY (Bone age)	-3.44±1.61 (-5.73 / -0.97)	0.18 ± 1.83 (-2.46 / -2.88)		p=0.0015		
GHST Peak GH response (ng/ml)	1.77±1.24 (0.1-4.4)	43.29±35.76 (12.9 - 121)		p=0.0003		
FOLLOW-UP TIME (year)	2.74±2.05 (0.33-6.09)					

Table 3. The comparison of the final findings of the patients between pituitary dwarfism and familial short stature and control groups during GH therapy

FINDINGS	PITUITARY DWARFISM A	FAMILIAL SHORT STATURE B	CONTROL C	A-B	A-C	B-C
AGE (year)	15.08±4.52	13.38±2.30	11.28±1.92	p>0.05	p=0.05	p>0.05
BONE AGE (year)	10.20±3.54	11.28±2.11	10.7±1.78	p>0.05	p>0.05	p>0.05
HEIGHT (cm)	135.62±14.42	140.16±8.84	145.11±13.67	p>0.05	p>0.05	p>0.05
HEIGHT SDS	-3.44±1.26	-2.15±1.29	0.18±1.15	p=0.03	p=0.003	p=0.003
HEIGHT VELOCITY (cm/year)	7.63±2.71	5.60±1.65		p>0.05		
HEIGHT VELOCITY SDS (Calendar age)	3.62±5.23	0.74±2.63		p>0.05		
HEIGHT VELOCITY SDS (Bone age)	1.96±3.65	0.18±1.83		p>0.05		
SERUM IGF-I (ng/ml) (During therapy)	74.5±72.4 (7.1 – 208)	349.9±251 (114.8-832.4)	299.5±294.1 (45.5-822.6)	p=0.003	p=0.02	p>0.05
SERUM IGF-I (Therapy for 4 days)	144.8±102.2 (36.5-386.9)	349.9±2.51	299.5±294.1	p>0.05	p>0.05	

Table 4. The comparison of the height SDS, height velocity and height velocity SDS of the patients pituitary dwarfism between at the beginning and after GH therapy

FINDINGS	BEGINNING OF GH THERAPY	AFTER GH THERAPY	P
HEIGHT SDS	-4.51 ± 1.56	-3.44 ± 1.26	0.007
HEIGHT VELOCITY	3.031 ± 1.52	7.63 ± 2.71	0.007
HEIGHT VELOCITY SDS (Calendar age)	-3.19 ± 1.76	3.62 ± 5.23	0.01
HEIGHT VELOCITY SDS (Bone Age)	-3.44 ± 1.61	1.96 ± 3.65	0.01

Table 5. The detection of the response of IGF-I to GH therapy in pituitary dwarfism group.

	DURING GH THERAPY	NO THERAPY FOR ONE MONTH		4 DAY GH THERAPY	P					
	A	GHST BASIC B	PEAK C	D	A-B	A-C	A-D	B-C	B-D	C-D
GH ng/ml		0.87 ± 0.68	0.87 ± 0.52					0.9		
IGF ng/ml	74.5 ± 72.4	30.1 ± 27.1	24 ± 28.1	144.8 ± 102.2	0.09	0.06	0.12	0.06	0.01	0.007
GH THERAPY DOSE (U)	13.33 ± 4.47*			14.22 ± 3.52**			0.7			

* Total dose weekly : 2-4 injektion

** 4 days total dose: 4 injection

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