Original paper

Evaluation of The Response of Children with Short Stature to A Six Months Treatment with Recombinant Human Growth Hormone

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Abstract

Background: Human Growth hormone (GH) is 191amino acids protein , gene located on long arm of chromosome 17. its secretion is under control of 2 hypothalamic hormones: growth hormone releasing hormone(GHRH) and somatostatin. Growth hormone is a major promoter of anabolism, its effects on growth are believed to be indirect ,being mediated through peptides called somatomedins or insulin-like growth factors (IGFs) that in turn mediate many of the growth promoting effects of Growth hormone . Recent advances have focused on biological actions of IGFs & their six well defined binding proteins (IGFBPs), the major one is IGF-BP3 which decreased in GH-deficient children. IGFs are GH-dependent serum peptide with potent metabolic & mitogenic activities believed to be responsible for growth effects of GH, they stimulate cellular replication & differentiation .

Objective: To evaluate the difference in the response of the children with short stature (of different causes) to a six months treatment with recombinant human GH .

Patients And Methods: this is a prospective study in which a total no. of 84 pt (with age ranging from 4-20 years) were included. They were presenting to the endocrine clinic in Al-Mansour teaching hospital for children in 2002 with short stature & growth delay. After the final diagnosis was made, all pt were treated by recombinant GH (in a dose of 0.1-0.2 unit/kg / day) by subcutaneous or intramuscular route at night time (7-8pm) , After completing 6 months of treatment with GH, the patients were evaluated again for height and height velocity, weight, bone age, height age, sexual maturity rate, testicles and phallus in male.

Results: There was no significant difference in response to the therapy between male and female ; the mean height velocity in male was 9.37 +/-3.99 cm / year (ranging from 1-19 cm) and the mean height velocity in female was 9.90 +/-4.39 cm / year ranging from 3-20 cm .

Conclusion: Growth hormone therapy is effective in increasing the height velocity in most patients with short stature and it should be initiated as early as possible to improve height as much as possible.

Keywords: growth hormone, pediatric, short stature.

Introduction

Normal somatic growth results from a complex interaction among genetic ,nutritional &hormonal factors, GH plays a major role in this process & other hormones including thyroid hormone, sex hormones &glucocorticoids as well as psychological factors exerts effects on the growth [(1)]. Human GH is 191a.a.protein, gene located on long arm of chromosome 17[(2)]. GH secretion is under control of 2 hypothalamic hormones (GHRH and somatostatin) [(3)]. Growth hormone is a major promoter of anabolism, its effects on growth are believed to be indirect ,being mediated through peptides called somatomedins or IGFs that in turn mediate many of the growth promoting effects of GH [(4)]. Recent advances have focused on biological actions of IGFs & their six well

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defined binding proteins (IGFBPs), the major one is IGF-BP3 which decreased in GH-deficient children[1,3] . IGFs are GH-dependent serum peptide with potent metabolic & mitogenic activities believed to be responsible for growth effects of GH, they stimulate cellular replication & differentiation [3,4]. growth hormone deficiency may be congenital (may be autosomal recessive or dominant or x-linked inheritance) or acquired (due to CNS tumors, cranial radiation, infiltrative disorders and trauma), it may be isolated or part of hypopituitarism [3,6]. the growth hormone may be not deficient but there is resistance to the hormone action leading to growth hormone insensitivity which may be primary (Laron syndrome) or secondary (due to malnutrition, diabetes, uremia, Alagille syndrome and GH antibodies [7]. The clinical manifestations of GH deficiency become apparent after 3-6 months of age and evident by slow growth velocity[6]. Other manifestations include immature appearance with high pitched voice resulting from immature larynx, poor musculature , delayed dentition and delayed bone age . Male neonate may have microphallus severe fasting hypoglycemia leading to seizure may occur because of decreased gluconeogenesis [6,8]. The diagnosis is made when GH response to 1 or preferably 2 provocative tests is abnormal and the child is growing with a subnormal growth velocity[9]. When the child fail a simple screening test (serum GH level of less than 10 ng/ml, more definitive testing is the next step[10] .All simulation tests should be performed only after thyroid function tests have been shown to have normal results because low thyroid function may suppress falsely the response of GH[11]. There are 2 groups of provocation tests [5,12]: physiological (exercise, sleep and postprandial) or pharmacological tests (clonidine, glucagon, arginine, Levodopa and insulin tolerance test), generally the child who is short and fail to mount a GH response of more than 10 ng/ml on at least one provocative test is considered GH-deficient and is then candidate for GH therapy[13]. The most important uses of growth hormone are :1- Growth hormone deficiency 2-Turner syndrome. 3-Chronic renal failure .4- Idiopathic short stature. 5-GH insensitivity. 6 - Children born small for date.7-Skeletal dysplasias 8-Syndromes associated with short stature (Noonan sndrome, Silver-Russel syndrome Prader-Willi sndrome and Down sndrome). 9-other uses of GH : patients with chronic illness & short stature like celiac diseases, galactosemia & nephrotic syndrome. Side effects of GH:1-Antibody production: occur very rarely and its presumed that these antibodies will not interfere with their own GH[14]. 2-Metabolic changes: such as diminished insulin responsiveness &glucose intolerance[15. 3-Cancer risk: several cases of leukemia have been reported in pt receiving GH but there is little evidence implicating GH as a cause[16]. 4-Pseudotumor cerebri: pt should have a complete ophthalmic evaluation if they report headache or visual disturbance [17]. 5- Other reported side effects: slipped capital femoral epiphysis, arthralgia, gynecomastia, mild edema & worsening of scoliosis[3,18] .

Objective

1- To evaluate the difference in the response of the children with short stature (of different causes) to a six months treatment with recombinant human GH.
2- To identify the side effects of GH therapy after six months treatment .

Patients And Methods

A total no. of 84 pt (with age ranging from 4-20 years) were included in this prospective study .They were presenting to the endocrine clinic in Al-Mansour teaching hospital for children in 2002 with short stature & growth delay. The following historical data were obtained: 1-Name ,age &sex of pt . 2-mode & date of

the first presentation. 3-birth history. 4-previous medical Hx. 5-previous growth Hx. 6- mentality &school performance.7-consanguinity. 8- family Hx of short stature. All pt were examined as the following: General examination, Measurements (height, height age, weight, occipitofrontal circumference, upper/lower segment ratio, height of parents if possible).

The investigations which were done for the pt were: 1- complete blood picture, blood urea, serum creatinine, blood sugar, serum electrolytes, general urine examination & general stool examination. 2- X-ray of the left wrist, hand & elbow for bone age. 3-Skull x-ray (sella turcica). 4- Antigliadin & antireticulin Ab and Small intestinal biopsy (if suspect celiac disease). 5- Abdominal ultrasound (if its indicated), 6-Chromosomal study & genetic consultation if indicated.7-Thyroid functions tests (T4 & TSH). 9- Growth hormone assay (basal & after provocation). 10- FSH, LH & estrogen level (if indicated). After that, the final diagnosis was made & all pt were treated by recombinant GH (in a dose of 0.1-0.2 unit/kg/day) by SC or IM route at night time (7-8pm). The patients & parents had received instructions about the way &route of injection of GH The patients were examined regularly at 4-6 wk interval. After completing 6 months of treatment with GH, the patients were evaluated again for the followings: 1-Height and height velocity as mentioned before. 2- Weight using the same weight calibrated scale which used before treatment. 3- Bone age. 4-Height for age. 5- Sexual maturity rate 6-Testicles and phallus in male. 7- Any side effects of the treatment. The patients were divided into 4 groups according to their age and into 9 different groups according to the etiological diagnosis.

Results

From the 84 patients whom included in this study , there were 58 (69%) male and 26 (31%) female with male to famale ratio of 2.2:1(table 1) which show also the distribution of cases according to the age groops (4 patients < 5 years , 20 patients from 6 to 10 yaers old, 45 patients from 11-15 years and 15 patients from 16-20 years old).

The mean height velocity was compared between the patients according to their sex and it was 9.73+/-3.99 cm/year (range 1-19) for male patients and 9.90 +/- 4.39 (range 3-20) for female patients (table 2).

The mean height velocity was also compared between the patients according to the chronological age where they divided into 4 age groups and the height velocity was compared between these groups as shown in table 3.

The patients divided according to the etiological diagnosis into 9 groups and the mean height velocity compared between these groups (as shown in table 4) .

Table 1. distribution of the cases according to the age groups and sex .

Age groups	GENDER				Total	
	Male		Female			
	No.	%	No.	%	No.	%
< 5 yrs	3	5.2	1	3.8	4	4.7
6-10 yrs	13	22.4	7	26.9	20	23.8
11-15 yrs	30	51.7	15	57.8	45	53.6
16-20 yrs	12	20.7	3	11.5	15	17.9
TOTAL	58	100	26	100	84	100

Table 2. the difference in response (height velocity) to the GH therapy according to the sex

Gender	Mean height velocity (cm / yr)	Standard deviation	Range (cm/yr)	P value
Male	9.73	3.99	1-19	Not significant
Female	9.90	4.39	3-20	

The response to the growth hormone therapy also compared between the patients according to the delay in bone age where they divided into 6 groups according to the years of delay in bone age and there was no significant difference between them (table 5) .

There were a side effects observed in our patients: 6 patients develop a local reactions to the therapy in form of redness, swelling and pain at site of injection , one patient develop arthralgia and 3 patients complaining severe headache. also there were a 7 patients who develop signs of increase intracranial pressure as shown in table 6.

Table 3. the difference in response (height velocity) to the GH therapy according to the age groups

Age group	No. & % of patients	Mean height velocity (cm / yr)	Standard deviation	Range (cm/yr)	P value
< 5 yrs	4 (4.7 %)	7.50	3.94	4-9	not significant
6-10 yrs	20(23.8%)	9.87	4.56	3-20	
11-15 yrs	45(53.6%)	9.89	3.92	1-19	
16-20 yrs	15(17.9%)	9.88	3.81	2-14	

Table 4. the difference in response (height velocity) to the GH therapy according to the etiological diagnosis

The diagnosis	No. and %	Mean height velocity (cm / yr)	Standard deviation	Range (cm/yr)	P Value
Idiopathic short stature	9 (10.7%)	9.11	3.79	2-13	<0.001
GH deficiency	54(64.28%)	10.40	4.00	3-20	<0.001
GH insensitivity	5 (5.95%)	6.83	1.94	4-10	<0.001
Hypopituitarism	3 (3.57%)	9.54	3.46	8-14	<0.05
Turner syndrome	3 (3.57%)	6.33	2.52	4-9	<0.05
Achodroplasia	2 (2.38%)	2.00	1.14	1-3	NS
Russell-Silver syndrome	2 (2.38%)	10.00	2.83	8-16	<0.001
Chronic renal failure	1 (1.19%)	4.00	.	.	.
Chronic illness (celiac disease)	2 (2.38%)	7.00	2.00	6-10	<0.05

NS = not significant

Table 5. the difference in height velocity according to the degree of delay in bone age.

Delay of bone age in years	No.	%	Mean HV (cm/year)	SD	Range (cm/year)	P value
No delay	9	10.7	8.33	3.5	4-15	not significant
1-2 years	25	29.8	9.28	4.30	2-20	
3-4 years	33	39.3	9.63	4.14	1-16	
5-6 years	12	14.3	11.58	2.99	6-15	
7-8 years	3	3.5	11.00	7.00	6-19	
> 8 years	2	2.4	9.00	1.41	8-10	
Total	84	100	9.80	4.05	1-20	

Table 6. the side effects of growth hormone which observed in our patients .

The side effect	No. of patients	%
1- Local reaction : redness , swelling , local pain	6	7.1%
2- Arthralgia	1	1.2%
3- Headache	3	3.6%
4- Effects on the eye (early signs of increase intracranial pressure)	7	8.3%

Discussion

Growth hormone therapy was given to children with short stature resulting from various causes for a period of 6 months and the response to the therapy represented by height velocity was evaluated. There was no significant difference in response to the therapy between male and female; the mean height velocity in male was 9.37 +/-3.99 cm / year (ranging from 1-19 cm) and the mean height velocity in female was 9.90 +/-4.39 cm / year ranging from 3-20 cm, this is agree with the result of a study done by Blethen SL in New York who found no significant difference between male and female in response to GH therapy[19]. The response also compared according to the chronological age by dividing the patients into 4 groups and there was no significant difference between these groups but there is slight increment in the mean height velocity with increasing age but not to a significant degree, this increment probably because of the effect of the puberty. The response to the GH therapy also compared between the patient according to the delay in bone age but there was no significant difference between them, so this indicate that the delay in bone age is a poor indicator for the response to the GH therapy , this was similar to the result of the study which is done by Zadik Z and associates who found no correlation of growth velocity during GH therapy with both chronological age and bone age[20]. The mean height before and after the GH therapy was compared between the pt in relation to the etiological diagnosis and there was significant increase in the mean height in all of the patients (P value was 0.05-0.001) except those with achondroplasia (P value was not significant) so we can clearly see that growth hormone therapy is significantly increase the height of the patients and this response may be a good indication for continuing the growth hormone therapy in these short children . The mean bone age of the patients before and after the growth hormone therapy was found to be significantly increase in patients with growth hormone deficiency, idiopathic short stature, hypopituitarism & chronic illnesses (P value 0.05-0.001) but there was no significant change in patients with achondroplasia (P value was not significant) and this was in the opposite of the result of study which is done by Low LC and associations in Hong Kong who found no acceleration of skeletal maturation after growth hormone therapy[21] but Zadik Z and associations study in Japan resulted in a nearly one year advancement after growth hormone therapy[20] which approximately similar to our results. There were a side effects observed: 1-Local reactions in form of redness, swelling & pain at the site of injection, this is probably caused by improper injection of the growth hormone being injected intradermally instead of SC injection so we instruct the pt again about the correct way for injection .2-Arthralgia was noted in one pt & it was very mild & no treatment was needed because it resolved spontaneously without stopping the therapy. 3-Three pt were having headache (one of them was having headache before the therapy) but the other 2 pt proved to be having signs of increase intracranial pressure by fundal examination . 4-Significant number of the pt (7patients=8.3%) develop fundoscopical changes indicating increase intracranial pressure so the therapy was stopped in these pt & they are going to be followed for any progression, this was similar to the result of study done by Rogers-AH[17].

Conclusion

Growth hormone therapy is effective in increasing the height velocity in most patients with short stature and response is not significantly differ according to the sex, chronological or bone age. A diagnostic trial of GH therapy may be the only method for selecting the short non-GH deficient pt who may benefit from

long term GH therapy .Early diagnosis & long term treatment with proper dose of GH may improve outcome in pt with GH deficiency. The possible benefit of GH therapy should be weighed against cost, availability & side effects .

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