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Variable response to growth hormone therapy in growth hormone deficient patients and role of insulin like growth factor one in monitoring response to therapy

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Abstract

Background and objectives: To find out the response to growth hormone therapy among growth hormone deficiency patients with different causes and to find out the role of insulin-like growth factor one in monitoring response. **Methods:** This retrospective study was done on fifty patients who received growth hormone for short stature due to different causes. The patients were enrolled in the study that was conducted from June 2015 to December 2015 in Helina center- Erbil. All details including history, examination, investigations, treatment and follow-up were revised. Investigations that have been sent for each patient were full blood count, thyroid function tests, bone age assessment, growth hormone stimulation and insulin like growth factor one. Follow-up for their response clinically and by investigations have been done after 3, 6 and 12 months and after two years from initiating growth hormone therapy. Patients were divided to three groups, patients on 25 mcg/kg/day therapy (Group One), patient on 30 mcg/kg/day (Group Two) and patients on 35 mcg/kg/day (Group Three). The response to growth hormone therapy of the three groups was compared. **Results:** Among those fifty patients, only five patients discontinued their treatment. Significant height gain was observed after two years of regular growth hormone therapy. We found that with increasing the dose of growth hormone, the patient gain more height, and had higher insulin-like growth factor one, with $p<0.05$ between the groups. The mean height gain over 2 years of growth hormone therapy was 11.16 cm in Group One and 16.25 cm in Group Three. **Conclusions:** We conclude that by giving growth hormone to short children for a period not less than two years, height will increase significantly. Giving higher allowed doses gives higher increment compared to lower doses and insulin like growth factor one is a good tool for follows-up response to therapy.

Keywords: Short stature; Growth hormone deficiency; Bone age; Insulin-like growth factor.

Introduction

Short stature is a term applied to a child whose height is twostandard deviations (SD) or more below the mean for children of that sex and chronologic age (and ideally of the same racial-ethnic group)[1]. Short stature can be promptly recognized only with accurate measurements of growth and critical analysis of growth data[2]. Short stature in childhood is a very common reason for referral to pediatric endocrinologists, although evaluation for growth inhibiting disorders is often indicated, most children with short stature are essentially healthy[3].Most short children do not have growth hormone deficiency, but because growth hormone deficiency is so highly treatable, it must be carefully considered and excluded[4]. Linear growth is maximum during infancy; 25 cm in first year, 10 cm/year in next twoyears. Subsequently, it gradually declines to 6–7 cm/year till puberty when again growth accelerates in sigmoid manner when it is around 10 cm/year[5]. Growth assessment requires accurate measurements of height and weight overtime, the measurement of parental height, pubertal staging, and the selection of appropriate group reference standards[6–8]. Growth hormone (GH) or somatotropin is produced and released by specialized cells (somatotrophs) in the anterior part of the pituitary gland. GH is needed for growth and has important effects on protein, lipids, and carbohydrate metabolism, which are accomplished directly as a result of GH binding to its receptor on target cells or indirectly primarily through insulin like growth factor 1 (IGF1), a hormone secreted from the liver and other tissues in response to GH. The majority of the growth-promoting effects of GH are through IGF1 acting on its target cells[9,10]. In the circulation, the IGFs are predominantly bound to binding proteins (IGFBP), which prolong the half-life of the IGFs and play a role in delivering them to target tissues[11]. Food and Drug Administration (FDA) approved indications for growth hormone therapy are GH deficiency, Turner syndrome, Noonan syndrome, Prader-Willi syndrome, idiopathic short stature, chronic kidney insufficiency, and small for gestational age[12,13]. The aims of this study were to demonstrate possible causes of short stature observe variable responses to different doses of growth hormone therapy and find out the role of IGF 1 as an indicator for response to GH therapy.

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Methods

This retrospective study was conducted in Helina Center for Special Needs in Erbil city (capital of Kurdistan Region-Iraq) from June 2015 to December 2015. Every single patient attending the center for managing his short stature has his own case file. All the details about management and follow-up were reviewed, including details of history, examination, investigation, treatment and follow-up. Investigations that have been done for each were full blood counts, thyroid function tests, bone age assessment, GH stimulation, and IGF1. The GHstimulation test measures the ability of the body to produce GH. The test took 2 to 5 hours. The first sample was drawn early in the morning. Normal value will exclude GH deficiency [14]. Normal peak value, at least 10 nanogram per milliliter (ng/mL), indeterminate, 5 to 10 ng/mL, subnormal, 5 ng/mL14. Unlike GH level, IGF1does not fluctuate greatly throughout the day for an individual person; IGF1 is used by physicians as a screening test for GH deficiency. Interpretation of IGF1 levels is complicated by the wide normal ranges, and marked variations by age, sex, and pubertal stage[15]. Inclusion criteria to receive GH in Helina center were low IGF1, Low-stimulated GH test and height less than third percentile for age and gender. Patients between 4 years up to closure of epiphyseal plate were included to receive GH deficiency.The candidates for GH therapy received regularly GH (somatropin-novonordisk) in dose 2535- mcg/kg/day subcutaneous injections, at night, 56- days/week at least for three months, (50 mcg/kg/day for Turner syndrome)[15]. Response was checked every threemonths and IGF1 was sent regularly. Sport encouragement and good diet regime were advised as well for all. We divided the patients into three groups according to the dose of GH; patients on 25 mcg/kg/day therapy (group one,18 patients), patient on 30 mcg/kg/day (group two, 20 patients) and 35 mcg/kg/day (group three 11 patients) Response to GH therapy was recorded in each group and compared with each other. The decision to stop GH treatment was made when (the patient) reached full pubertal development (Tanner stage 5 + >16 for males, >15 for females) and complete fusion of the epiphysis, growth velocity <1 cm/year in the last year, appearance of complications, and normalization of IGF1. For each patient, name, age, gender, mode of delivery, gestational age, birth weight, height and weight before starting treatment, height gain in 6 month, 1 year, and 2 year, GH level, IGF1 level before and after therapy, thyroid function test, complete blood count, parental height, any other disease in patient and his family, dose and route of GH were recorded. Data were analyzed using the Statistical Package for Social Sciences (SPSS, version 19). Student's t test was used to compare between means of two groups. One-way analysis of variance (ANOVA) was used to compare the means of three or more groups. A post hoc test (LSD) was used after ANOVA to compare means of each two groups separately. A p value of ≤ 0.05 was considered statistically significant.

Results

Fifty patients were included in this study. Out of those patients, only five patients discontinued their treatment;two patients because of normalization of IGF1 and the other three because of poor gains of height in response to treatment.The mean age (+ SD) of the sample was 11.76 + 3.37 years, ranging from 4 to 19 years, with a median of 11.5 years. The mean age (± SD) of starting treatment was 9.28 ± 2.9 years. Eighteen percent of the sample-started treatment at the age of 46- years, whereas 14% started treatment at the age of 13 years or after. More than half (54%) of the sample were males.Regarding the causes of growth hormone deficiency, among 50 patients 44 patients (88%) were diagnosed as isolated GH deficiency, two patients (4%) born small for gestational age, one case operated for craniopharyngioma, one case of renal tubular acidosis, a case of thalassemia major who was transplanted for bone marrow, a case of turner syndrome, and 3 patients had hypothyroidism, beside GH deficiency.The mean height gain in response to 35 mcg/kg/day was significantly higher than the mean height gain in response to 25 and 30 mcg/kg/day ($p<0.05$). This applies to all the studied periods, Table 1.

Table (1): Mean height gain by dose.

Height gain (cm)	Dose	No.	Mean height gain (cm)	SD	P (ANOVA)	LSD comparisons	p (LSD)
Gain in 6 months	25	18	2.72	0.75	0.001	25X30	0.684
	30	20	2.88	1.27		25X35	< 0.001
	35	11	4.45	1.44		30X35	0.001
	Total	**49**	**3.17**	**1.33**			
Gain in 1st year	25	18	5.64	1.89	0.001	25X30	0.396
	30	19	6.16	1.86		25X35	< 0.001
	35	11	8.50	1.72		30X35	0.002
	Total	**48**	**6.50**	**2.12**			
Gain in 2nd year	25	16	5.19	2.43	0.007	25X30	0.218
	30	18	6.06	1.36		25X35	0.002
	35	10	7.90	2.28		30X35	0.026
	Total	**44**	**6.16**	**2.23**			
Total height gain after 2 years	25	16	11.16	3.91	.002	25 X 30	0.271
	30	18	12.44	2.89		25 X 35	0.001
	35	10	16.25	3.19		30 X 35	0.006
	Total	**44**	**12.84**	**3.82**			

Table 2 shows no significant differences in the mean height gain according to the age of starting treatment ($p > 0.05$). This applies to all the studied periods.

Table (2): Height gain in different ages by age of starting treatment.

Gain in 6 months	4-6	9	3.667	1.323	
	7-9	17	3.088	1.349	
	10-12	17	3.412	1.450	0.400
	13+	7	2.571	1.272	
	Total	**50**	**3.230**	**1.371**	
Gain in 1st year	4-6	9	7.556	1.928	
	7-9	17	6.118	2.212	
	10-12	17	6.765	2.107	0.277
	13+	6	5.667	2.066	
	Total	**49**	**6.551**	**2.132**	
Gain in 2nd year	4-6	9	7.167	2.550	
	7-9	16	5.438	2.128	
	10-12	15	6.467	2.057	0.286
	13+	5	6.100	2.133	
	Total	**45**	**6.200**	**2.217**	

Every single patient who received growth hormone has been followed up by IGF1. The mean IGF1 before treatment was 56.48(34.08) ng/ml, increased to the mean of 96.45 (31.20) ng/dl after treatment. There was significant increase in the level of IGF1 after treatment ($P<0.05$), as shown in Table 3.

Table (3): Mean IGF1 before and after treatment.

IGFI (ng/ml)	Mean	SD	No.	P value
IGF1 before treatment	56.48	34.08	50	< 0.001
IGF1 after treatment	96.45	31.20	50	

After following up of patients by IGF1, our result showed that with increasing the dose of growth hormone the IGF1 level became higher, as shown in Table 4.

Table(4): Mean IGFI after treatment by dose of growth hormone.

Dose	No.	Mean IGF1 (post)	SD	P (ANOVA)	LSD comparisons	P (LSD)
25	18	92.15	21.15	0.017	25X30	0.783
30	20	89.55	21.13		25X35	0.014
35	11	120.29	47.27		30X35	0.007

Discussion

This study found that, with treatment of growth hormone there would be a significant height increment. A Canadian randomized control trial was published recently, they randomly assigned 154 children to treatment with GH or no treatment and both the groups were observed until the adult height was reached. They were able to follow up 61 of 76 treated patients and 43 of 78 controls to adult height and observed a 7.2 cm difference between the two groups. The mean duration of treatment was 5.7 years[16]. We found that height gain was directly proportional to the dose of the therapy; our result agreed with Wit et al. study[17]. The study found that there was no significant difference between those who received growth hormone therapy in earlier age vs. later in age. While other studies found that the final height gain is proportional with early therapy, as found by Blethenet al[18]. This disagreement may be due to that we took height gain only in two years of therapy and not up to puberty, so we did not have the final adult height of our patients.Insulin like growth factor 1is a cofactor, which is highly dependent on GH release in a normal person. Our study demonstrates that there was a significant increase in IGF1 after 2 years therapy with GH therapy, this result was parallel to Cohen, et al, as they found higher IGF1 after 2 years of treatment with GH[19]. This study also found that the raise in level of IGF1 is proportional with the dose of GH therapy, this result is comparable) to that of Cohen et al[20] who reported similar results.We also foundno significant difference in linear growth gain between genders, different age groups and causes of GH deficiency. This result is consistent with that of Cut fieldet al[21].

Conclusions

Growth hormone therapy has a major role in promoting height in GH deficient patient. Giving GHin regular bases for 2 years or more will increase height significantly in all growth hormone deficient patientsregardless of thecause of short stature. The higher dose of recombinant GH gives the higher height increment and higher levels of IGF1. Insulin like growth factor one is a good tool for following up those who receive growth hormone therapy.

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