The response to Growth Hormone Therapy in Isolated Growth Hormone Deficiency

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Abstract

Objective: to study the response of Growth hormone therapy in children with short stature due to isolated growth hormone deficiency.
Sample: six hundred forty eight patient with short stature were enrolled in this study.
Method: six hundred forty eight patient with short stature attending Central Teaching Hospital for children Baghdad/ Iraq, were recorded and all patients were investigated to exclude other disease like diabetes, hypothyroidism, celiac disease, turner syndrome, renal failure, achondroplasia,..etc. with a total of 48 patients due to these causes were excluded from the study. So the remaining patients were 600 only those exposed to our study. All children investigated for growth hormone basal level and after provocation by clonidine done for one time .
Results: We found that the basal level of growth hormone was less 0.5 microgram (µg)/liter (L), 0.5 -1 µg/liter and more than 1 µg /liter in 25%, 38% and 37% respectively in our sample, while the results after provocation were less than 5, 5-10 and more than 10 µg /liter in 60%, 28% and 12% respectively in our sample. The effect of growth hormone in one year therapy the increment in height was less than 4 cm in 22% of our patients, from 4-8 cm in 50%, and more than 8 cm in 28 % and we found that the male patients were 384(64%), and the female patients were 216(36%),with peak difference between bone age and chronological age was more than 2 year for both sex and most of the patientś age was more than 15 years.
Conclusion: Most patients with isolated growth hormone deficiency had basal growth hormone level 0.5 – 1µg/L, while the provocation level was less than 5µg/L and the effect of growth hormone therapy on height maximally 4-8 cm in proximately 50% of the patients and more than 8 cm in 28% after one year treatment. Patients with isolated Gh deficiency showed good response to therapy with growth hormone recombinant in a dose 0.1 mg /kg /day
Key ward: Gh, Growth hormone

الخلاصة

هدف البحث:دراسة الاستجابة للعلاج بهرمون النمو عند الأطفال قصار القامة بسبب نقص هرمون النمو المنعزل.
طريقه البحث:تم جمع ٦٤٨ طفل قصير القامة المراجعين للعيادة الاستشارية في مستشفى الطفل المركزي التعليمي في بغداد /العراق. وبعد إجراء الفحوصات ألشعاعيه والمختبرية تم استبعاد الأطفال الذين تبين إن قصر قامتهم لا يعود إلى نقص هرمون النمو من الدراسة كالمصابين بالحالات التالية (داء السكري،نقص الغدة الدرقية،حساسية الحنطة، متلازمة تيرنر، عجز الكلية، داء التقزم.....).وكان عددهم ٤٨ مريضا ، وبذلك يكون عدد المرضى الذين خضعوا للدراسة ٦٠٠ مريضا.تم إجراء فحص مستوى هرمون النمو الأساسي وكذلك بعد إجراء التحفيز بواسطة إعطاء مادة الكلوندين لمرة واحدة فقط وذلك لعدم توفر الإمكانيات لتكرار الفحص بعد التحفيز .وكان مستوى الهورمون الأساسي كالأتي اقل من ٠.٥ مايكرو غرام /لتر، ومن ٠.٥—١ ،وأكثر من ١، في ٢٥% ،٣٨% ، ٣٧% من المرضى على التوالي. إما النتائج بعد التحفيز كالأتي : اقل من ٥ مايكرو غرام /لتر ، ومن ٥--١٠ ، وأكثر من ١٠ ،في ٦٠%،٢٨%،١٢% من المرضى على التوالي.
النتائج :مقدار الزيادة في الطول بعد سنه كاملة من العلاج بهرمون النمو بجرعة (٠.١mg /kg/day)كانت كالآتي :اقل من ٤سم، من ٤- ٨سم، وأكثر من ٨سم ،في ٢٢%،٥٠%،٢٨% من المرضى.وكانت نسبة الذكور هي ٦٤%، بينما الإناث

٣٦%،وكان أقصى فرق بين العمر الحقيقي وعمر العظم هو أكثر من ٢ سنه،لكلا الجنسين، وكان اغلب أعمار المرضى أكثر من ١٥ سنه.

التوصيات: الأطفال قصار القامة بسبب نقص هرمون النمو المنعزل فقط اظهروا استجابة واضحة للعلاج

Introduction

Growth hormone (Gh)

Gh is the most a abundant hormone in the pituitary gland. It is a single chain Alfa helical nonglycosylated polypeptide with 191 amino acids & two intramolecular di-sulfide bonds with molecular weight of 22 kDa. This mature hormone accounts for 75% of the Gh produced in the pituitary gland[1]. Gh is encoded by the Gh-1 gene. It is part of a 50- kb cluster of five genes located on human chromosome 17q [2].

Gh secretion

Gh secretion is under the control of two hypothalamic hormones: Gh releasing hormone (GhRH) and somatotropin release inhibiting factor (S-RIF), also known as somatostatin (sst)[3].

Gh action

At least 50% of circulating Gh is bound to Gh –binding protein (Gh- BP), which is the extracellular domain of the Gh receptor (Gh-R) found circulating in the serum as a soluble form[4]. Many of actions of Gh are mediated by insulin -like growth factors (IGFs) or somatomedins which were first identified by their ability to incorporate sulfate into rat cartilage[5]. Because of their resemblance to pro-insulin, these peptides were named Insulin – like growth factors[6]. The actions of Gh on extra uterine growth are primarily through stimulation of production of IGF-1 ,a basic 70 amino acid peptide[7]. Human fetal serum IGF-1 level is relatively low and is positively correlated with gestational age in newborn, serum IGF-1 levels are 30% - 50% of adult levels.

During childhood, serum IGF-1 levels gradually increase, reaching adult values at the onset of puberty[8,9]. Gonadal steroids increase IGF-1 production, contributing to the pubertal growth spurt. During puberty, serum IGF-1 levels peak achieving 2-3 times adult value[10,11]. After adolescent, serum IGF-1concentrations decline gradually with age[12,13]. Both systemic IGF-1, and local IGF-1 predominantly produced by the liver[14-16], stimulate longitudinal bone growth by increasing osteoblastic activity and increased collagen synthesis in bone[17].

GH DEFICENCY

Hypopituitarism can be caused by anything that damage the hypothalamus, pituitary stalk, the congenital Gh deficiency has been reported 1:4000 and 1:10000 live births[18,19].

Growth failure is the most common sign of Gh deficiency presenting in infancy and childhood. Children with mild Gh deficiency usually present after the 6th month of age, when influence of maternal hormones wane[20]. They generally have normal birth weights, with slightly below average lengths[21]. The growth rate of child with Gh deficiency will progressively decline., they developed an increase peri-abdominal fat and decreased muscle mass, and may also had delayed dentition, thin hair, poor nail growth & high pitched voice[20-22].

Severe Gh deficiency in newborn period may be characterized by hypoglycemia, conjugated hyperbilirubinemia, as well as small phallus in boys, consistent with multiple anterior pituitary hormone deficiencies[20].

ACQUIRED FORM OF HYPOPITUITARISM

1. Head trauma can damage the pituitary stalk & infundibulum and can lead to the development of transient & permanent diabetes insipid us, as well as other hormonal deficiencies[23,24].
2. Breech delivery there are association between hypopituitarism & complicated perinatal course[18,25,26].
3. Infiltrative condition; histiocytosis & sarcoidosis[27-29].
4. Metabolic condition, hemochromatosis[30,31].
5. Neoplastic condition; craniopharngioma, hypothalamic-astrocytoma.
6. Hypothalamic or pituitary tissue can be destroyed by the mass of supra-sellar tumour or by surgical resection[32].
7. Cranial irridiation during treatment of brain tumour or acute lymphoblastic leukemia .Clayton et al. reported that 84% of children who receiving greater than 3000 cGy to hypothalamo-pituitary area had evidence of Gh deficiency five years after irradiation[33].

CONGENITAL FORM HYPOPITUITARISM

Cranial malformation such as holoprosoncephaly, septo-optic dysplasia (SOD), and midline cranio-cerebral or mid-facial abnormalities can be associated with anomalies of pituitary gland Embryonic defects such as pituitary hypoplasia, pituitary aplasia, and congenital absence of pituitary gland can also occur[34]. Include:

1. Gh-RH Receptor mutations.
2. pituitary transcription factor mutations.
3. GH Gene mutations.
4. GH-R mutations.

Laron dwarfisim is an autosomal recessive disorder characterized by clinical feature of severe Gh deficiency but with normal to high levels of h-Gh after provocative testing[35]. Plasma IGF-1 level are low and do not respond to exogenous h-Gh[36,37], Recombinant IGF-1 can be used for treatment[38,39].

DIAGNOSIS OF GH DEFICIENCY

The diagnosis of Gh deficiency in childhood must be based on criteria;

1. Evaluation of the Gh –IGF axis is indicated in children with height below two standard deviation scores (SDS) and growth velocity over at least 6 months below 10 – 25th percentile, in whom other causes of growth retardation have been ruled out[40] .
2. peak serum Gh below 10 ng/ml after two stimulation test[41].
3. we must assess IGF-1 and its binding protein IGF-BPs[1].

Gh STIMULATION TESTS

Gh is secreted episodically, mostly during rapid eye movement sleep. Radioimmunoassays (RIAS) and immunometric assays are the most commonly used laboratory- techniques for determination of Gh levels .Estimations performed by RIA use polyclonal-antibodies, there is variety of pharmacological tests to assess the Gh secretary capacity of the pituitary gland[40]. They are expensive , not free of side effects, require fasting conditions as high glucose levels inhibit Gh secretion. Gh provocative tests have been divided into 2 groups ;

1. screening tests including (exercise, levodopa and clonidine)
2. definitive tests include (arginine, insulin, glucagon){42,43 }

CLONIDINE

Clondine is an Alfa –2 adrenergic agonist that increase Gh-RH secretion and inhibits (SRIF) .Blood pressure monitoring is necessary as hypotension may occur.

Dosage 5μg/kg (maximum 250 μg.).Samples of blood Gh are drawn at 0 . 30 mints[44].

EXERCISE TEST

It has been implemented as a screening test. 3 – 4 hrs of fasting should be precede the test. Twenty minutes of mild to moderate exercise should be performed with final heart rate exceeding 120 beats min for the test to be valid. Although it is safe and inexpensive .it had little uses because some children fail to response to increase Gh at 20 and 40 mints[45] The following table 1. Show the criteria of provocation tests[41].

Table 1. The criteria of different provocation tests

No.	test	Dose	Time of peak effect	Side effect
1	Insulin induced hypoglycemia	0.05- 0. 1 IU/kg iv bolus	30 – 60 min	Sever hypoglycemia
2	clonidine	0.125mg/m² oral .	60 – 120 min	Drowsiness, hypotension
3	L- dopa / propranolol L- dopa	 125mg b .w. <13.5kg 250mg b .w.>31.5<31.5kg 500mg >31.5 kg oral	 60 – 120 min	 Headache & nausea &emesis
4	propranolol	0.75mg //dose/ oral	120 –180 min	Induced asthma late hypoglycemia
5	glucagon	0.03mg/kg (max 1 mg) sc or im	120 – 180 min	Late hypoglycemia
6	Arginine hydrochloride GhRH	0.5 g /kg iv over 20 min 1 or 2 μg /kg iv bolus	40 – 70 min 30-60 min	Late hypoglycemia flashing
7	exercise	20 min of moderate exercise	20 – 40 min	Exhaustion ,post-exercise induced asthma

IGFs

The IGFs are related Gh –dependent factors that mediate many of anabolic & mitogenic actions of Gh. Gh induces the expression of IGF –1 in liver & cartilage[46]. Low levels are also reported in children especially in those less than 5 years of age with malnutrition, hypothyroidisms, renal failure, hepatic disease and diabetes mellitus[47,48].

Patients and methods

Anthropometric measurements of height, weight, skin fold thickness and upper to lower segment ratio the measurement were plotted on growth centile charts of Tanner, the height below 2 SD below the mean and growth velocity below 10th centile was considered short. This is retrospective study in the Central Teaching Hospital for children in Baghdad, short stature cases was referred from other hospital and primary health care centers and medical institution from Baghdad, Ambar, Salah –dein city. 648 cases of short stature collected, Investigations were done accordingly and other causes of short stature other than isolated growth hormone are diagnosed and excluded from our study like hypothyroidisms, achodroplasia, hypochodroplasia, pan hypopituitarism craniopharyngioma, mucopolysacharides, polycystic kidney , diabetes mellitus , renal tubular acidosis, turner syndrome, anemia, rickets, celiac disease and ellis van crevel syndrome. All these cases were excluded from the study, as in the table- 2

Table 2. The different causes of short stature

Number of patients	Cause of short stature
5	hypothyroidism
12	anemia
1	Ellis van crevel syndrome
1	rickets
1	Congenital heart disease
10	Celiac disease
3	Achondroplasia
2	hypochodroplasia
2	panhypopituitarism
2	Diabetes mellitus
1	Craniopharyngioma
1	Mucopolysacchriode
٢	Polycystic kidney
1	Renal tubular acidosis
4	Turner syndrom
48	Total number

We measure the height of all children by skilled person and after taken the development history other like, gastroenteritis problem, respiratory like (cough dyspnea, cyanosis) central nerves system like headache, blurred vision, cardiovascular symptom like palpitation, cyanosis after complete physical examination including weight, height, skin fold thickness, heart rate, respiratory rate, blood pressure, general and systemic examination.

We calculate mid parental height father and mother height and we consider child short stature if height is below 3rd centile or more than 2SD deviation below the mean. The bone age was recorded by the radiologist

Results

The result show that the growth hormone basal level as such (<0.5 , 0.5-1, >1 µg /l) in our patients 25%, 38% and 38%) respectively as shown in figure 1

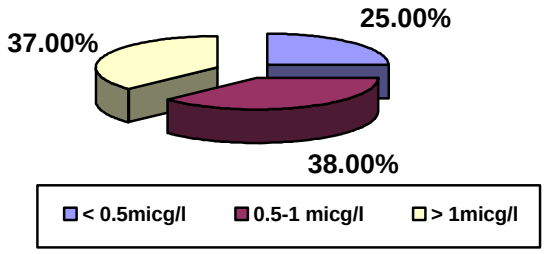

Figure 1. Growth hormone basal level

While the growth hormone level after provocation was (<5, 5-10, >10 µg/l) in our patients as (60%, 28%, 12%) respectively as shown in figure 2.

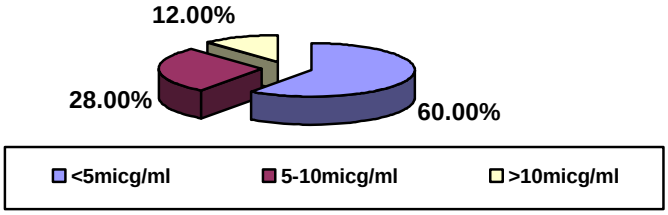

Figure 2. Growth hormone provocation test

Regarding sex difference we found that male patients constitute 64% (384) while the female 36% (216) as shown in figure 3.

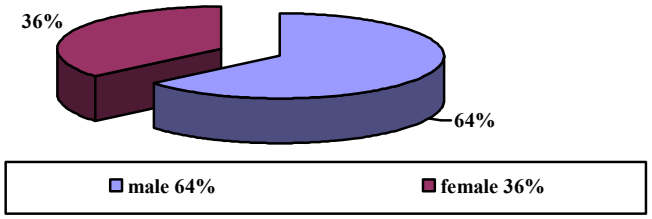

Figure 3. Sex distribution in short stature

Regard the different between the bone age and chronological age we found that the male patient (<1, 1-2, >2 years) as (32,90, 262) respectively while in female (18, 54, 144) as shown in table 3 .

Table 3. The difference between bone age and chronological age in each sex.

Age in years	male	%	female	%
< 1 year	32	5%	18	3%
1—2 years	90	15%	54	9%
> 2 years	262	44%	144	24%
total	384	64%	216	36%

Regarding the percentage the difference between bone age and chronological age in general (male and female) was (<1, 1-2, >2 years) (5%, 22%, 73%) respectively as shown in figure 4.

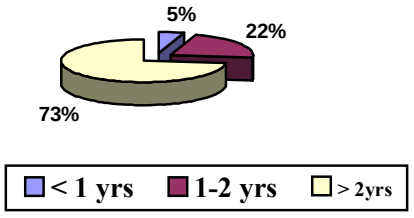

Figure 4. The percentage between bone age and chronological age

Regarding the male distribution according to the age we found that (< 5, 5-10, 10- 15, > 15 years) as (7%, 30%, 18%, 45%) respectively as shown in figure 5 .

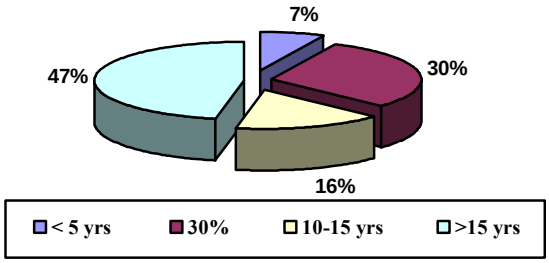

Figure 5. Male distribution according to age

Regarding the female distribution according to the age we found that (< 5, 5-10, 10- 15, > 15 years) as (10%, 30%, 9%, and 51%) respectively as shown in figure 6.

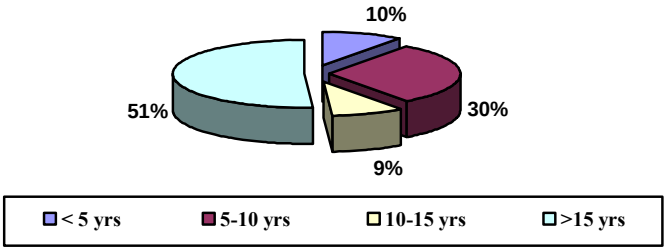

Figure 6. Female distribution according to age .

Response to therapy during the first 6 month we noticed that the response as (< 4, 4--8, > 8 cm) in our patients (59%, 38%, and 3%) respectively as shown in figure 7.

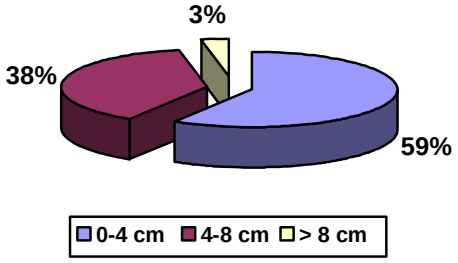

Figure 7. Response to therapy during the first sixth months

While the response to the therapy after 1 year duration in our patient we noticed that the increment in height (<4, 4--8 , > 8 cm) in our patients (22%, 50%, and 28%) respectively as shown figure 8 .

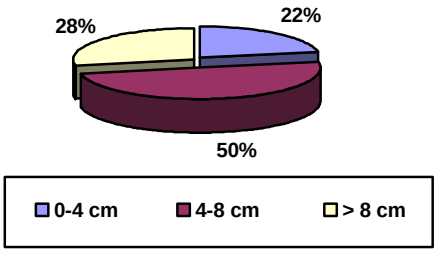

Figure 8. Response to therapy within one year of therapy

Discussion

The growth hormone level after single provocation test in current study (<0.5, 0.5 – 1, > 1 ng /ml) was (60% , 28%, 12%) respectively which in harmony with several workers[49-51], in spite that they used two provocation test and documented that GH level (< 10µg/ml) after two test.

The sex distribution, most of the studies show that male dominancy (♂ /♀ =1.7/1) as in refs. {52,49,50,53}, which compatible with our results.

Bone age ,the difference was (> 2 year) between the bone age and chronological age in{ 50, 54,55}.which is in harmony with our study result (73%).o: f the patient, while the response to therapy ,there was a significant increase in growth velocity averaging (10 cm/year) during the first year of therapy, this response decline each year later but it was more than pretreatment rates[56-58], all these are too much higher than our study results, and the explanation to that may be due to patient compliance, drug availability ,and efficacy. low dose of drug (0.1 mg/ml) may be the cause ,in regard to high dose therapy (0.2-0.7mg/ml) as in[50,53,56,59].

The peak age of growth hormone deficiency,the first peak at 5 year which compatible with school entry as the length of the child was compared with their peers {60,50,61}, which showed wide discrepancy with our study ,the explanation to that may be due to ignorance of the families about the problem in our society that lead to late diagnosis. While the second peak occurs in girls aged 10-13year, and boys aged 12- 16 year which possibly to delay puberty[50,60,61], all these were compatible with our study results.

Conclusion

1. Short stature is medical problem but had psychological complications on the patient life, which was a treatable problem. As the patients with isolated growth hormone deficiency show good response to therapy with growth hormone recombinant in a dose of 0.1mg⁄kg⁄day.
2. early diagnosis is essential for early treatment and better results to therapy.

Recommendation

1. The length &height of the child should be carefully measured & regular follow up, and the patient should be referred to endocrinological clinic if any suspension of growth failure.

2. All staff of out patient should be well trained how to measure the height and length of our patients.
3. Early detection of short stature is very important as early as possible before puberty for best chance for good results.

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