The Efficacy of Growth Hormone Therapy on Children with Growth Hormone Deficiency Treated with Recombinant Human Growth Hormone

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Abstract

The use of growth hormone (GH) in clinical endocrine practice is expanding and its role in the treatment of various clinical conditions is increasingly appreciated. Concurrently, concerns have been raised about the ethnical, economic, safety and efficacy of growth hormone and this study in this direction. This study is conducted to determine the growth response to growth hormone(GH) therapy in growth hormone deficient patients(GHD) either partial or complete selected from those who registered in pediatric endocrinology clinic at Central Teaching Hospital for Children in Baghdad and the effect of other factors as age, gender, birth weight, chronological bone age…..etc. A prospective study was conducted on 160 patients with age 3-12 years selected from 1400 patients with age 1-18 years registered in pediatric endocrinology clinic at central teaching hospital for children presented with short stature subjected to full physical examination preceded by medical history and accurate measurements including parents then they screened for causes of short stature including hormonal ,chromosomal and radiological assay to confirm the growth hormone deficiency after that treated with recombinant growth hormone from 1st June 2008 and 1st December 2008 during this period the patients followed monthly according to filing system. The height velocity before treatment was 3.5±1.2cm/y after 6 months of therapy was 8.5±3.6cm/y.There was no significant difference in the height velocity regarding the sex, age, partial or complete GHD and the degree of the bone age delay in contrast to birth weight which had significant positive correlation with height velocity response among of 160 patients 136 (85%) achieved adequate response. This study indicates a significant response in linear growth in patients with GHD after treatment with recombinant GH with positive relationship with birth weight so effort & resources needed to achieve availability of the drug, related equipments, laboratory tests & trained personnel. This study is preliminary one and we hope further expanded studies in this subject in the future.

Introduction

Growth hormone promotes linear growth; the somatotropic effects occur partially through stimulation of the production of insulin-like growth factor 1 (IGF-1). IGF-1 produced primarily by the liver circulates throughout the body, where as IGF-1 produced in the growth cartilage acts locally as a paracrine-autocrine growth factor (6, 7). In addition ,the diverse metabolic actions of GH include its anabolic and lipolytic effects GH also induces insulin resistance (6, 7, 1) .

GH has now been shown to be produced throughout adult life and to have important physiologic and metabolic effects long after final height has been reached (1, 2, 3, and 4). The causes of GHD are: Congenital, Midline embryonic defect: septo-optic dysplasia (SOD), cleft palate, pituitary aplasia/hypoplasia. Transcription factor mutations: GH1, Pit-1, PROP1, HESX1.Acquired, Pituitary/hypothalamic tumour: craniopharyngiomas, germinoma, pinealoma. Trauma: surgery, perinatal, Infiltration; histiocytosis, lymphoma, leukaemia.

Infection: bacterial, viral, fungal. Irradiation: intracranial, nasopharyngeal

tumours. Cranial or cranio-spinal irradiation in acute leukaemia. Temporary failure: emotional deprivation, peri-pubertal or hypothyroidism. Idiopathic (1, 2). Sever short stature is defined as a height more than 2 standard deviations below the population mean. The evaluation for GHD in a short child should not be initiated until other causes of growth failure, such as hypothyroidism, chronic systemic disease, Turner syndrome, skeletal disorders and psychosocial deprivation have been considered and appropriately excluded (1, 2, 3). Growth Hormone (GH) has been used to treat children with GH deficiency (GHD) for more than 40 years. Human GH was originally obtained from cadaver pituitaries and was available in limited quantities (1, 3, 4,5). In 1985, studies indicated that pituitary-derived GH was the likely source of contaminated material (prions) responsible for the development of Creutzfeldt-Jakob disease- a slowly developing, progressive, fatal neurologic disorder (1, 2, 4).

Biosynthetic GH initially became available for prescription use in USA in 1985.Human GH of recombinant DNA origin with an amino sequence identical to GH of pituitary origin is produced commercially by several pharmaceutical companies (1, 3, and 4).The US FDA has approved GH for use in the following pediatric conditions 1.GHD. 2. Turner Syndrome. 3. Chronic renal failure insufficiency. 4. Small for gestational age or intrauterine growth retardation including Russell ``Silver syndrome. 5. Prader-Wille syndrome. 6. Continued height deficit at puberty (1, 3, and 4).

Subjects and Methods

This is a prospective study conducted in Central Teaching Hospital for Children in Baghdad between 1st June 2008 and 1st December 2008 because availability of (GH: Serono Saizen 1.33mg = 4 unit) during this period. One hundred sixty patients with age range; (3-12) years selected from 1400 patients with age range; (1-18) years included in this study considered GHD after fulfilling the criteria which adopted by multicenter, clinical trial of recombinant GH in GHD by department of pediatrics-University of Tubingen West Germany the criteria includes: Height ≤2.5 SD of mean for chronological age, Height velocity ≤2 SD of mean for chronological age or < 5 cm/year at age of 3-12 year, Peak plasma GH: *total GHD < 5ng/ml *partial GHD (5.1-10 ng/ml) after provocation test by clonidine (1,2,3,4).

All the patients presented with short stature disorder to Pediatric Endocrinology Clinic in Central Teaching Hospital for Children in Baghdad subjected to full physical examination preceded by medical history and accurate measurements including parents then subjected for the following screening investigations: *Blood; Full blood count (FBC) film,* IgA antiendomysial and tissue transglutaminase antibodies (screening for chronic gastrointestinal disease as malabsorption)

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*Creatinine,urea and electrolytes ,calcium and phosphate (screening for renal disease).*T4 and TSH, GH basal and after provocative stimuli , cortisol,prolactin ,ACTH, LH,FSH.* Chromosomal assay in selected case as Turner Syndrome ,Down's syndrome ,Prader Willi syndrome. *Urine: general and culture and urine osmolality in selected cases .

*Diagnostic imaging: bone age all cases (2,3,4), abdominal ultrasound for selected cases, skeletal survey if dysplasia suspected and CT scan for selected cases. Jejunal biopsy: in some cases .Hormonal assay, celiac screening and chromosomal study was done in diabetic centre in Alyarmuk Hospital and other investigations with diagnostic imaging were done in Central Teaching Hospital for Children in Baghdad. A data sheet for each patient was filled with a file included: the name, age, sex, type of delivery (NVD or CS) gestational age, birth wt, consanguinity, bone age, height and height SD before and after starting therapy, complete GHD or partial GHD and height velocity before therapy. A control group of One hundred sixty children with normal height with age range of 3-12 year whom visited the general pediatric clinic in the same hospital for other causes .A data sheet included: type of delivery, gestational age , birth weight , consanguinity followed for 6 months before initiation the therapy in patient & control group.

Recombinant GH was given to all patients from in a dose of 0.3 mg/kg /week divided daily at bed time SC with closed supervision from us at the beginning of therapy then we followed them monthly for checking and giving the therapy after training the parents and the patients about the rout of injection and possible side effects. In each visit height, weight measurement and other data was taken and fixed in each patient file.

Results

From the total of 160 patients the sex distribution was (112) males and (48) females.In control group (76) male and (84) female .The degree of consanguinity compared relative to non relative was 120/40 in comparism to 61/99 in control group. The type of delivery compared as NVD to CS was 136/24 in the patients and 126/34 in control group. The birth weight according to gestational age divided as* normal for gestational age (NGA), *small for gestational age (SGA) and *small with unknown gestational age. The result was 126,21 and 13 in patients group and 130,18 ,and 12 in control group table (1).The height velocity increased from 3.5±1.2 cm/year before treatment to 8.5 ±3.6 cm / year after (6) months of treatment with significantly P value as in table(2) & figure (1) .This significant increment in height velocity was compared in different age group (range 3-12 y) ,different bone age (range 1-10 y) table (3), sex difference table(4) and figure (2)and different degree in delay of bone age (range 2-8) table (5) ,degree of GHD either partial or complete table (6) and figure (3) and the degree of response in relation to birth weight correlated with gestational age table (7) & figure(4).

The result shows no significant difference regarding the response to GH therapy between sex difference (male/female ratio range in GHD patients range 2.3:1 & in control group 1:1.03 respectively) , consanguinity(3:1 among patients group& 1:1.63 in control group respectively) , delay in bone age and degree of GHD respectively as shown in tables (1,3,4,5,6) and figures (2,3). With exception to that the birth weight there is a significant difference between (NGA) and (SGA) with p- value (0.007) table (7) and figure (4).

Discussion

It is obvious from this study that there is a significant response in the linear growth after treatment with recombinant GH therapy in patients with GHD by increment of height velocity from 3.5 ± 1.2/year before treatment to 8.5 ± 3.6 cm/year after 6 months of treatment .This response is approximately similar to that in a study of Rasmunssen LH et al in 1989 (12) in Denmark & slightly more than the study of Ituro Hibin et al in 1987 in Japan (13) & Hernan Dez.Min 1991 in Spain (14), but slightly less than result in the study of Kaplan SL. et al in 1986 in England (15), J.R. Sierich et al in 1987 in west Germany (16) and Shiyf, Bao et al in 1990 in China(17). From the results, there are different responses in different countries this may attributed to racial factors, type of recombinant GH or the duration of the study.

The Study shows that the chronological age , bone age and its delay , height and its SD prior to treatment are poor predictors for degree of response to GH therapy in patients with GHD this result similar to study of J.M.Wit et al 1986 (18) & Rank Mb et al 1991(19). For sex difference there is no significant difference in reponse to GH therapy because there is no sex difference for concentration of endogenous GH as mentioned by Jansson et al 1982 (9) and the half life of exogenous GH is the same for both sex. The result is similar to the study of J.R Sierich et al in 1987 (16). Regarding provocative test there is no significant difference in response to GH therapy neither in complete GHD nor partial GHD. This is similar to the results of study of J.M.Wit el al 1986 (18). provocative test fails as a predictor to growth response in patients with GHD because the result of this test can vary in the same patient over a time and the resulting of GHD children as adults often does not sustain the original diagnosis (Caccairi et al 1994 and Tauber M. et al 1997)(19,20).

A bout birth weight and its correlation to gestational age because of the difficulty in obtaining the exact information

, the patients had classified in two groups those with weight >2.5 kg considered NGA and those with weight <2.5 kg considered SGA.

The majority of patients included in this study with GHD 79% (126 from160) were considered normal for gestational (NGA) and because birth weight has been shown to have a great influence on the response of growth hormone therapy in this study (P value 0.007) which is similar to the study of Lassare C.et al 1991 (21).

The explanation is that children with SGA could be relatively insensitive to the action of either endogenous GH or to IGf-1 (Lassare C et al 1991) (21). Male to female ratio range in the GH deficient patients was 2.3: 1 and this approximately is similar to J.R. Sierich in 1987(16) and Rasmussen in 1987 study but it differs from the ratio in control group male / female ratio range 1: 1.03 . Regarding consanguinity it is higher among patients group 3:1 than control group 1:1.63. The percentage of CS to NVD was 15% to 85% in patients group and 21% to 79% in control group reverse to the result of Albertson-Wikland et al 1983 (22) which showed 16.6% to 83.4% and 10.4% to 89.4% in patient group and control group respectively.

The percentage of small for gestational age to normal for gestational age 13% to 79% respectively approximately similar to John C. et al 1998(23) result were 19% to 81% respectively and similar to control group. Reference to the criteria of this study the significant response to the therapy was achieved by 85% (136 from 160) and 15% (24 from 160) fail to achieve adequate response This may explained as: SGA patients need higher doses of GH 0.48mg/kg/week in divided doses(1,2,3), The patients may not follow the proper instructions regarding the dose ,frequency or the cooling chain ,Wrong diagnosis because lack of many hormonal assay e.g.: IGF-1 ,GHBP….etc. , Intercurrent illnesses during therapy period might interfere with the response. In conclusion the efficacy of GH therapy in GHD patients is so effective which significantly related to birth weight correlated to gestational age.

As this subject has socioeconomic & medical aspects because the patients are short statures and the drug is expensive and medically requires trained personnel oriented in the diagnosis of the cases, side effect of the drug and the response to it.

So this subject needs more concentration from the Iraqi Ministry of Health and other responsible Authorities regarding availability of GH & other hormonal assay tests as (IGF-1,GHBP) ,health education, training medical & nursing staff including the post and under graduate medical students Expanding the pediatric endocrinology clinics to cover at least the main governorates and to follow the newborn neonates with low birth weight by the primary health centers with cooperation with pediatric endocrinology clinics.

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Table 1: shows sex distribution, degree of consanguinity, type of delivery and birth weight in GHD patient & control group.

Patients group	GHD	Control group
1.sex distribution -male	112(70%)	76(48%)
female	48 (30%)	84(52%)
2.degree of consanguinity-relative	120(75%)	61 (38%)
not relative	40 (25%)	99 (62%)
3.type of delivery-NVD	136(85%)	126(79%)
-CS	24 (15%)	34(21%)
4.birth weight related to GA		
-NGA	126(79%)	130(81%)
-SGA	21(13%)	18(11%)
-small with unknown GA	13 (8%)	12(8%)

Table 2: Shows height velocity response before treatment and after 3 and 6 months respectively.

No. of patients	Height velocity Mean±SD	Range
Pretreatment 160	3.5± 1.2 cm /y	1.5-4.7
After 3 months R/160	9.2 ±3.2 cm/y	2-16
After 6 moths R/ 160	8.5 ±3.6	2-16

T=9.944 P-value=0.00001 Significant

Table3: shows degree of response in regard to chronological age.

Age in years	No. of patients	Mean± SD	Range
3- <4	12	9.57 ± 3.5	4-15
4- <5	16	9.18 ±3.5	6-16
5 -<6	21	8.0 ±3.8	2-16
6 -<7	12	8.17 ±3.0	3-12
7 -<8	14	9.22 ±3.7	3-14
8 -<9	15	8.8 ±3.3	4-16
9 -<10	22	8.81 ±3.2	2-14
10- <11	13	8.5 ±4.3	2-16
11 -<12	21	8.93 ± 4.3	2-16
12 - 13	14	9.3 ±4.8	2-16

F = 0.181 P-value =0.99 not significant

Table 4 Shows response regarding sex difference

Sex & No. of Patient	height velocity cm/y	Range
Female :59	8.9 ±3.9	2-16
Male :101	8.7 ±3.4	2-16

T =0.275 P value=0.78 not significant

Table 5: shows response according to delay in bone age

Delay bone age in years	No.of patiezts	Height velocity cm / year mean ± SD	Range cm
<2 years	45	8.8 ±3.5	2-16
2-<4	60	8.68 ± 2.9	3-16
4-<6	31	9.95 ±4.9	2-16
6-< 8	13	4.5 ±3.5	2-16
> 8	11	2	3-16

F- value=2.225 P value =0.071 not significant

Table 6: shows degree of response in partial and complete GHD

Provocative test	No. of patients	Height velocity cm /y mean ± SD	Range in cm
Complete GHD < 5	90	8.56 ±3.8 cm/y	2-16
Partial GHD >5-10	70	9.2±3.38 cm/y	2-16

T =0.913 P value =0.635 not significant

Table 7: shows degree of response regarding birth weight correlated with gestational **age**

Birth weight /gestational age	No. of patients	Height velocity cm /y Mean ±SD	Range
Normal for gestational age	126	9.45±3.4	2-16
Small for gestational age	21	6.4 ± 4	2-8
Small with unknown age	13	6.0 ± 2.4	2-8

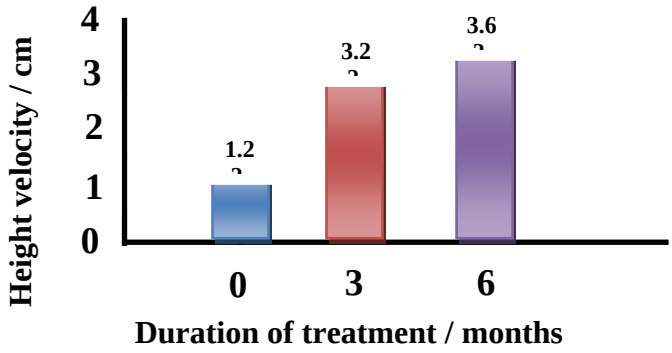

Fig 1 shows height velocity response before and after 3 and 6 months treatment respectively

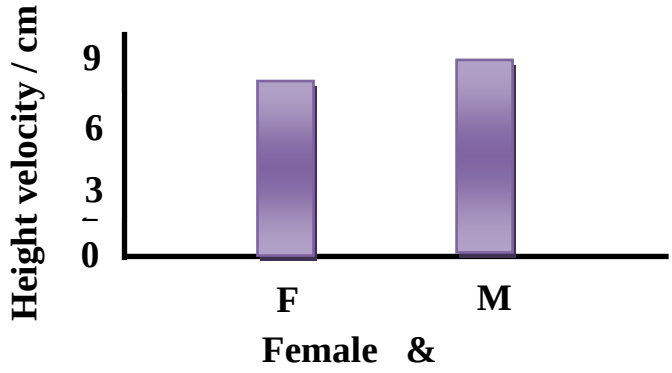

Fig 2: shows response in regard to sex difference

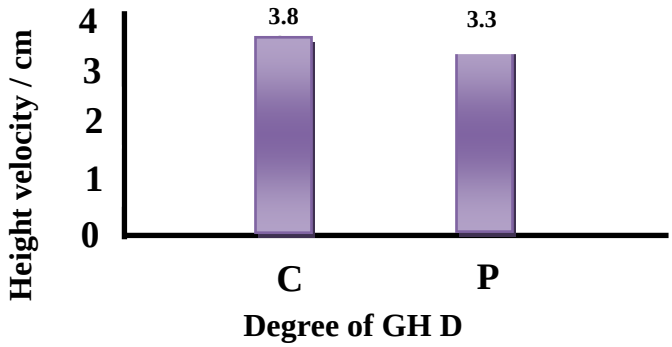

Fig 3: shows degree of response in partial and complete GHD