Response of Height Measurements to Growth hormone therapy in Short Children with Growth hormone Deficiency

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Abstract:

Background: longitudinal assessment of growth is essential child care.

Objective: to find out the response of growth in term of the number of the standard deviations below the mean of height for age and sex (Z score) (HAZ) to the recombinant human growth hormone therapy in short children with growth hormone deficiency and others.

Patients & Methods: A prospective study was done on 325 children; their age range was 1-19years, referred to growth hormone clinic of Central Teaching Hospital for Children / Baghdad with short-stature for their age or with slow growth. The study included only those children on regular recombinant human growth hormone (rhGH) therapy for (6 months - 4 years), for the period between 1st of October 1997 till 1st of March 2003. Evaluation included: detailed medical history, physical examination (included height measurements) and laboratory tests such as blood count, general urine examination, thyroid function, growth hormone assay (basal and after simulation with clonidine 75-100mcg/m^2), bone age and chromosomal analysis from peripheral blood, and those who were diagnosed as growth hormone deficiency, were commenced on growth hormone therapy in a dose of (0.24-0.3 mg / kg /wk).

Results: has shown a highly significant increase in the Z-score of height for age (HAZ) of children with growth hormone deficiency in response to (rhGH) therapy in a dose (0.24-0.3mg/kg/wk) from (-4.28±1.99) to (-1.86±2.48), while the patients with Turner syndrome from (-4.33±2.02) to (-1.94±2.52), when treated with (rhGH) in a dose (0.3-0.37mg/kg/wk), so as in patients with growth hormone deficiency and celiac disease who were on gluten free diet for one year, but the response was less in children with achondroplasia or with others like Down syndrome and Silver-Russell syndrome. The response was more significant in the prepubertal than pubertal age groups.

Conclusion: earlier identification of short children due to growth hormone deficiency & earlier treatment to have a better response & similarly earlier identification of short females with Turner syndrome.

Key words: growth hormone deficiency, height measurement, short stature.

Introduction:

Prior to the use of growth hormone therapy the final adult height of the children with growth hormone deficiency (GHD) were between 130-140 cm, but with the growth hormone therapy their final adult height is achieved within the range of normal population in 85% of them, the response depends on the onset of the treatment & on the midparents height [1, 2 ,3] .

The synthetic growth hormone was firstly approved in several European countries & Japan in 1988. In 1995\1996 it has been used in adult with GHD. In 1996 it has been used in chronic renal failure in Europe [1, 3].

In Japan it has been used in skeletal dysplasia in 1997 [3].

The first trial of the Turner Xx in 1997 & approved in Europe, Japan & in USA in 1999\ 2000[2, 3].

The principle reason for treating short children with growth hormone is the hope that their quality of life can be improved and that opportunities for individual fulfillment can be realized [1].

There is one genetic syndrome known as Floating–Harbor syndrome (FHS) is clinically characterized by short stature, retarded speech development, delayed bone age, and typical faces. Four cases with celiac disease have been described previously. In two other cases, autosomal dominant inheritance has been suggested, in the study done by Penaloza,-J-M, et al. they described a boy with clinical features of FHS and celiac disease [4].

In children, growth hormone is necessary for body growth. When maturity is reached and the epiphysis close bone growth stops [5].

It was found that the instance of GHD are approximately 1/4000 children [6].

Patients & Methods:

A prospective study was done on 325 children [boys 218 constituting 67%, and girls 107 constituting 33%] their age range was 1-19 years (mean age 9.8±3.9) who were referred to growth hormone clinic of Central Teaching Hospital for Children / Baghdad with short-stature for their age or with slow growth. The total cases were grouped according to their age as prepubertal (12years&below) and pubertal age group (13-19years). The prepubertal group (accounted for 222 cases constituting 63.3%), including (boys 140 constituting 63.1% & girls 82 constituting 36.9%), The other group was pubertal age group (accounted for 103 cases constituting 36.7%, as boys 78 constituting 75.7% & girls 25 constituting 24.3%). The study included only those children on regular recombinant human growth hormone growth

(rhGH) therapy for (6 months - 4 years). The period of study between 1st of October 1997 till 1st of March 2003.

The following information was taken:

1- Date of birth.
2- Detailed medical history.
3- Complete physical examination.

Anthropometric measurements were done:

-Height measurement by stadiometer of Sicca (France made, sensitive to 10mm), was done by technician &supervise by the researcher, the average of three reading were taken. The assessment of height measurement was done according to Tanner & Whitehouse growth charts by taking the Z-score (How many standard deviations of the child measurement taken below the mean for age and sex according to these charts).

-Other anthropometric measurements were done like body weight and (fronto-occipital circumference for each child).

- The height of the parents & siblings were taken.

The child was considered short when his height was -3 standard deviation scores (SDS) below the mean for age and gender (-3 Z-scores).

For children who can not stand or recline completely (e.g. those with spina bifida or contractures) arm span provide a reliable alternative for longitudinal assessment of long bone growth.

4-Skeletal maturation typically is determined by the bone age obtained from an A.P radiograph of the left hand & wrist joint.

5-Assessing sexual maturity ratings (SMRs) stage according to Tanner & Whitehouse growth charts.

6-Growth hormone assay (basal and provocation test, one hour estimation after stimulation with clonidine 75-100 mcg/m^2) were done for all patients.

7-Other endocrinal investigation include; TSH, T4, (free & total), for each child.

8-Complete blood count, blood urea and general urine examination (GUE) were done for all children.

9- Assessing the different etiological causes of short stature was done by;

a- Karyotype for all girls to excluded Turner syndrome.

b-Other investigation: like S. creatinine to exclude chronic renal failure. Jujenal biopsy (in those with non specific gastrointestinal manifestation, poor gain in weight for height & for age &/or anemia) for exclusion of celiac disease.

10-The treatment with (rhGH) has been given in a dose of 0.24-0.3mg/kg/wk to all groups except in girls with Turner syndrome the dose were 0.3-0.37mg/kg/wk in divided dose subcutaneously [3 , 7].

11- Familial short stature, constitutional delay and nutritional short stature were excluded from this study.

12- Criteria for stopping treatment include growth rate less than 1 inch / y, and bone age of greater than 14year in girls and 16year in boys, they were adopted by John S. Parks [8].

Results:

Among the total number of (325) children with short stature the diagnosis were as follow, 95.1% have GHD, 1.8% Turner syndrome, 1.2% GHD & celiac disease, 0.9% achondroplasia, 0.3% Down syndrome, 0.3% Silver-Russell syndrome & 0.3% for panhypopituitarism as shown in (table 1).

Table 1: The distribution of cases according to etiology.

Etiology	No	%
Growth Hormone Deficiency	**309**	**95.1**
Turner Syndrome	**6**	**1.8**
GHD & Celiac Disease	**4**	**1.2**
Achondroplasia	**3**	**0.9**
Down Syndrome	**1**	**0.3**
Panhypopituitarism	**1**	**0.3**
Sliver-Russell Syndrome	**1**	**0.3**
Total	**325**	**100%**

Table (2) shows that all cases of short-stature [325cases] have a highly significant response to growth hormone (GH) with increase in HAZ from -4.32±2.02 to -1.94±2.52 (p<0.0001).

The total cases were grouped into 222 cases constituting (63.3%) as prepubertal age group and has shown a response to (GH) of highly significant increase in HAZ from -4.51±2.05 to -1.79±2.63 (p<0.0001). The other group was pubertal age group 103 cases constituting (36.7%) has shown also a highly significant increase in HAZ from -3.94±1.9 to -2.26±2.23 (p< 0.0001), as shown in (table 2).

Also table (2) has shown that the response to (GH) therapy of prepubertal age group was more significant than the pubertal age group.

The percentage response to (GH) therapy (Percentage difference= (after treatment–base line)/base linex100) is higher in prepubertal age group (60.3%) than the pubertal age group (42.6%).

According to the sex difference there were no variation in response to (GH), as there was a highly significant increase in HAZ in prepubertal males from -4.04±1.93 to -1.61±2.54 (P<0.0001), and in prepubertal females from -5.29±2.02 to -2.10±2.76 (P<0.0001). In regarding pubertal age group there was a highly significant increase in HAZ in males from -3.74±1.78 to -2.07±2.03 (P<0.0001), and in females from -4.55±2.18 to -2.85±2.73 (P<0.0001) as shown in (table 2).

Table 2: The distribution of height measurements before and after GH therapy according to age and sex.

Age **Sex**	**Before GH therapy Mean±SD (Range)**	**After GH therapy Mean±SD (Range)**	**Mean % difference**	**Comparing before and after**
Pre-pubertal (n=222)	-4.51±2.05 (-11.6 – 0)	-1.79±2.63 (-8.6 – 5.0)	60.3%	P<0.0001*
Male (n=140)	-4.04±1.93 (-10 – 0)	-1.61±2.54 (-8.5 – 5.0)	60.2%	P<0.0001*
Female (n=82)	-5.29±2.021 (-11.6 - -1.5)	-2.102±2.76 (-8.6 – 4.0)	60.3%	P<0.0001*
Pubertal (n=103)	-3.94±1.9 (-9 - -0.4)	-2.26±2.23 (-8 – 4)	42.6%	P<0.0001*
Male (n=78)	-3.74±1.78 (-8.6 - -0.4)	-2.07±2.03 (-8 – 4)	44.7%	P<0.0001*
Female (n=25)	-4.55±2.18 (-9 - -1.3)	-2.85±2.73 (-8 – 2.7)	37.4%	P<0.0001*
Total (n=325)	-4.324±2.019 (-11.6 - 0)	-1.938±2.52 (-8.6 - 5.0)	55.2%	P<0.0001*

*Highly significant

Table (3) has shown a highly significant increase (56.5%) in HAZ of children with GHD in response to (GH) therapy in a dose (0.24-0.3mg/kg/wk) from -4.28±1.99 to -1.86 ±2.48 (P<0.0001), while the patients with Turner syndrome the HAZ increase (55.2%) from -4.33±2.02 to -1.94±2.52 (P<0.0001) when treated with (GH) in a dose of (0.3-0.37mg/kg/wk), & in patient with GHD and celiac disease who were on gluten free diet for one year, the HAZ increase from -4.0±2.16 to -2.45±2.14 (P<0.0001), but the response was less in children with achondroplasia (17.8%) or with others like Down syndrome and Silver-Russell syndrome.

As comparing the response to growth hormone therapy there is no significant difference between children with GHD , Turner syndrome and GHD & celiac disease (P>0.05), but there is significant

difference between children with GHD & those with achondroplasia (P<0.05, the GHD group response better than the achondroplagic patients) as shown in (table 3).

Table 3: The distribution of height measurements before and after GH therapy according to etiology.

Etiology	Before GH therapy Mean±SD (Range)	After GH therapy Mean±SD (Range)	Mean % difference	Comparing before and after
Growth Hormone Deficiency (n=309)	-4.28±1.99 (-11.6 – 0)	-1.86±2.48 (-8.6 – 5)	56.5%	P<0.0001**
Turner Syndrome (n=6)	-4.33±2.02 (-11.6 – 0)	-1.94±2.52 (-8.6 - 5)	55.2%	P<0.0001**
GHD & Celiac Disease (n=4)	-4.0±2.16 (-6.0 - -1.0)	-2.45±2.14 (-5 - -0.4)	38.8%	P<0.0001**
Achondroplasia (n=3)	-6.97±2.37 (-9.5 - -4.8)	-5.73±2.48 (-8.5 - -3.7)	17.8%	P<0.0001**
Down Syndrome (n=1)	-8.0	-7.2	-	-
Panhypopituitarism (n=1)	-6.3	-6.3	-	-
Sliver-Russell Syndrome (n=1)	-4.0	-4.0	-	-
Turner Compared with GHD	P>0.05	P>0.05		
GHD & Celiac Compared with GHD	P>0.05	P>0.05		
Achondroplagic. Compared with GHD	P<0.05*	P<0.05*		

*significant
**Highly significant

Discussion:

Three hundred twenty five children were referred from three governorates –Baghdad governorate (Al-Karkh district), Al-Anbar governorate and Salahdeen governorate, GHD constitute 1/10000 children, it is lower than that reported by Ronald W. Gotlin, et al. they reported that the instance of GHD are approximately 1/4000 children [6].

This lower figure can be explained on assumption of lower identification of cases during economic sanction because of the general deterioration in the health systems as primary health care, investigation needed for diagnosis, etc. So many of those children with GHD were disadvantaged as the growth hormone was not available during the time of economic sanction, so the cases were accumulated at pubertal age group.

In this study Turner syndrome cases were account for 1.8%, which was similar to that reported by Shu, et al. A national screening and referral program which was launched in Taiwan; they found that Turner syndrome account for 1.4% [9].

Also in this study the use of recombinant human somatotropin (rhGH) in a dose of 0.24-0.3mg /kg / wk in divided dose subcutaneously increase the growth rate to about 5-10 cm during the first 6 months up to one year of starting therapy in patient with GHD and these were similar to that reported by Wit, -J-M, study [3].

Regarding girls with Turner syndrome, growth hormone therapy led to a good response by increase their height(3.5cm-10cm/y), which is similar to that reported by Van-Pareren, et al. , Ning, -G; et al. and Fang,-J; et al. [10, 11, 12,]

Final height achieved in some of patients with GHD and Turner syndrome, ranging around -2 SDS of the normal population, and these were similar to that reported by Cave,-C-B, et al., Chaussain,-J-L, Schonau,-E, et al. and Wasniewska-M, et al. [7, 13, 14, 15]

Regarding patients with GHD and celiac disease who were on gluten free diet for one year, they showed a good response to GH by increase their height (2-4cm/y), no reported similar studies to be compared.

In this study the response was more significant in the prepubertal than pubertal age group but there are no studies to compare with.

Conclusion and Recommendation:

Since when reaching maturity and epiphysis closed, bone growth stops, it is essential for earlier identification of short children and earlier treatment to have a better response, in particularly children with GHD, and girls with Turner syndrome.

It needs to optimize recombinant human growth hormone therapy by individual dose adjustment and this contributes to improved overall outcome.

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