RESPONSE VARIABILITY TO GROWTH HORMONE THERAPY IN CHILDREN WITH SHORT STATURE

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ABSTRACT

Background: A clear definition of growth response after intervention with therapies such as GH is lacking. **The aim of this study** is to evaluate growth response to GH therapy and factors affecting it in children with short stature. ***Patients and methods:*** the present study was a prospective study that carried on 100 children referred from all-over Upper Egypt to growth clinic at Assiut Health Insurance Clinics, 74 of them were diagnosed as Isolated Growth Hormone Deficiency (IGHD), 6 of them were diagnosed as Multiple Pituitary Hormonal Deficiency (MPHD) and 20 of them were diagnosed as Turner Syndrome. All children had inclusion criteria of age between 4-12 and duration of GH treatment at least one year. Full history taking and physical examination with special concern to the anthropometric measurements initially and follow up every 3 months was recorded. Also records of the children were be reviewed for initial investigations, routine general laboratory tests, which include (complete blood picture, stool examination, complete urine analysis, renal and liver function tests), Thyroid profile free thyroid hormones (FT3, FT4), thyroid stimulating hormone (TSH), growth hormone (GH) secretion by provocation test (insulin tolerance test), Karyotyping when indicated, X-ray of the left wrist and hand, left elbow or shoulder joint for bone age determination. All patients received rhGH with a standard dose of 0.6 IU/kg/week. The calculated dose per week was divided for six days and given subcutaneously at night. ***Results:*** There were good response to GH therapy among IGHD cases by increase their height (5-12 cm) during 1st year of treatment. There was highly significant difference in IGHD cases between their height SDs before treatment (-4.94±0.98) and after 1 year of treatment (-4.21±1.03) *P*-value = 0.0001. Regarding MPHD cases GH therapy lead to a good response by increase their height (7.5-12 cm) during 1st year of treatment. The difference between their height SDs before treatment (-4.94±0.98) and after 1 year of treatment (-4.00±0.48) was close to significant (*P*-value =0.068). Among Turner syndrome cases GH therapy lead to a good response by increase their height (3.5-8.5 cm) during 1st year of treatment. There is highly significant difference in Turner cases between their height SDs before treatment (-5.74±1.4) and after 1 year of treatment (-5.33±1.33), *P*-value=0.0001. There is positive (+ve) correlation coefficient between change in height SD after 1 year of therapy for all study groups and bone age delay (r= 0.243), target height (r =0.203) and change in height SD after 6 months (r= 0.793).

Kay words: IGHD. MPHD, short stature, turner, rhGH.

INTRODUCTION

Short stature is defined as height below 3rd centile or less than two standard deviations (SDs) below the median height for that age and sex according to the population standard; or even if the height is within the normal percentiles but growth velocity is consistently below 25th percentile over 6–12 months of observation. Approximately 3% children in any population will be short **(Lifschitz, 2006).**

Biosynthetic growth hormone (GH) has an amino acid sequence identical to human growth hormone (hGH) and is made by bacteria or other cells using recombinant DNA technology. In the United States, the Food and Drug Administration (FDA) licensed biosynthetic growth hormone for treatment of growth hormone deficiency in 1985 and the drug received regulatory approval in other countries shortly thereafter, With the availability of a virtually limitless supply of biosynthetic growth hormone the therapeutic indications for GH use gradually increased over the following years **(Sadeghi, 2008).**

A clear definition of growth response after intervention with therapies such as GH is lacking, Although GH has been used for treating short stature in GH deficiency (GHD) and other conditions for more than 40 year, criteria for defining satisfactory GH response targets have never been developed. The range of GH response is large, differences can be attributed to diagnosis, age, GH dose, parental height (Ht), compliance, intercurrent illness, other (endocrine) therapies, and still poorly defined molecular and biochemical factors that may include the structure and concentration of GH receptors, the robustness of the post-receptor signaling cascade, IGF-I transcriptional and translational efficiency, and epiphyseal responsiveness to GH, IGF-I, and other factors **(Bert et al, 2013).** The aim of this study is to evaluate growth response to GH therapy and factors affecting it in children with short stature.

PATIENTS AND METHODS

The present study was a prospective study that carried on 100 children referred from Upper Egypt to Growth clinic at Assiut Health Insurance Clinics during the period from 1st January 2011 to 31th December 2013. All children had inclusion criteria of age between 4-12 and duration of GH treatment at least one year. These children were diagnosed and recieved recombinant growth hormone treatment. There was no conflict of interest regarding GH

therapy. All children had stature more than - 2.5 SDs below the mean for the same age and sex. 74 of them were diagnosed as IGHD (GH peak value less than 10 ng/ml in Insulin provocation test), 6 of them were diagnosed as MPHD and 20 of them were diagnosed as Turner Syndrome. Children with age more than 4 and less than one or more of the following criteria were excluded from the study: children with any chronic disease, children with skeletal dysplasia, duration of GH treatment less than one year or refusal of participation.

Methods:

After approval of ethical committee in the faculty of medicine Al Azhar Univresity and after obtaining verbal consent from the parents for participation of their children in this study, *the following data were collected*: full personal history, detailed birth history, feeding history, drug history, family history, physical examination *and* anthropometric measurements:-

Height was measured twice and neared to the next millimetre using Harpenden Stadiometer, ***height velocity*** in cm/year is the variable that describes the patient's one year velocity, ***Weight*** of the patients was measured using balances and recorded in decimal of kilogram, ***weight and height SDs*** is calculated using Z score figures **(Centers for Disease Control and Prevention, 2010),** ***BMI*** is calculated using formula [BMI=Weight (Kg) /Height (m^2)]**(Keys et al,1972)** and ***Target height*** was calculated by the method of **(Tanner *et al*,1970)** taking the average of mother's and father's height after addition of 13 cm in boys or subtractions of them in girls. Records were be reviewed for initial anthropometric measurements and the follow up every 3 months. Also records of the children were be reviewed for initial investigation:

Routine general laboratory tests, if needed:- which include complete blood picture, stool examination, complete urine analysis, renal and liver function tests. Thyroid profile (FT3, FT4, TSH):- Thyroid stimulating hormone (TSH) was estimated by immunoradiometric assay (IRMA), while FT3 and FT4 were estimated by radioimmunoassay kits from Diagnosis Product Corporation. GH secretion by provocation test (insulin tolerance test):- GH level was estimated by immunoradiometric assay (IRMA). Dose of insulin was 0.1 U/kg I.V. Blood samples were drawn at 0, 20, 40, 60, 90, 120 and, sometimes at 180 min if hypoglycemia was delayed.

Karyotyping: was done when indicated. X-ray of the left wrist and hand and elbow or shoulder joint to estimate the bone age using (Tanner Whitehouse no.2 method) **(Tanner et al,1983)**

Treatment protocol: All patients received biosynthetic growth hormone therapy. Three products are available in Egypt; Norditropin (NovoNordisk, Denmark), Genotropin (Pharmacia and Upjohn, Sweden) and Humatrope (ElliLilly, USA). All patients received rhGH with a standard dose of 0.6 IU/kg/week. The calculated dose per week was divided for six days and given subcutaneously at night **(Wit and Rekers-Mombarg, 2013)**.

RESULTS

Table (1): Anthropometric Measurements at the start of Treatment for all Studied Groups.

Groups	IGHD (n= 74)	MPHD (n= 6)	Turner (n= 20)	Significance		
				P1	P2	P3
Weight SDs at start of treatment						
Mean ± SD	-2.95 ± 0.83	-2.58 ± 1.23	-3.38 ± 0.88	0.328	0.019*	0.255
Median	-3.0	-2.45	-3.3			
Range	-5 to -1.2	-4.2 to -1.2	-5 to -2			
Height SDs at start treatment						
Mean ± SD	-4.94 ± 0.98	-4.83 ± 0.52	-5.74 ± 1.40	0.860	0.032*	0.076
Median	-4.78	-4.85	-5.45			
Range	-6.78 to -3.2	-5.33 to -4.3	-8.4 to -4.4			
Body Mass Index (BMI)						
Mean ± SD	16.36 ± 2.70	17.58 ± 6.27	16.20 ± 2.79	0.965	0.833	0.998
Median	16.25	15.9	15.35			
Range	12 to 23.6	12.1 to 26.4	12.4 to 22			

P1: Comparison between IGHD and MPHD groups
P2: Comparison between IGHD and Turner groups
P3: Comparison between MPHD and Turner groups
**** Highly statistical significance**
IGHD: Isolated Growth Hormone Deficiency
MPHD: Multiple Pituitary Hormonal Deficiency
*** Statistical significance**

Table (1) showed a statistically significant difference for both weight and height SDs between IGHD and turner groups.

Table (2): Maximum Stimulated Growth Hormone Level at the start of Treatment for all Studied Groups

Growth hormone level (µg/L)	IGHD (n= 64)	MPHD (n= 6)	Turner (n= 30)	P1	P2	P3
Mean ± SD	1.66 ± 1.67	1.07 ± 1.34	7.70 ± 5.95	0.377	0.000**	0.002**
Median	0.91	0.58	5.0			
Range	0.09 to 6.1	0.12 to 3.0	2.9 to 21.0			

P1: Comparison between IGHD and MPHD groups
P2: Comparison between IGHD and Turner groups
P3: Comparison between MPHD and Turner groups
IGHD: Isolated Growth Hormone Deficiency
MPHD: Multiple Pituitary Hormonal Deficiency
**** Highly statistical significance**

Table (2) showed a statistically significant difference between turner group and each of IGHD and MPHD regarding maximum stimulated growth hormone level at the start of treatment

Table (3): **Anthropometric Measurements at Follow-up for all Studied Groups**.

	IGHD (n= 74)	MPHD (n= 6)	Turner (n= 20)	P1	P2	P3
Height velocity after 1 year				0.595	0.000*	0.010*
Mean ± SD	9.35 ± 2.78	10.13 ± 2.78	6.20 ± 1.55			
Median	8.0	9.0	6.25			
Range	5 to 12	7.5 to 12	3.5 to 8.5			
Height SDs after 6 months				0.965	0.000*	0.016*
Mean ± SD	-4.45 ± 1.00	-4.35 ± 0.50	-5.54 ± 1.31			
Median	-4.4	-4.1	-5.25			
Range	-6.47 to -2.5	-5.1 to -4.1	-8.2 to -4.2			
Height SDs after 1 year				0.791	0.000*	0.016*
Mean ± SD	-4.21 ± 1.03	-4.00 ± 0.48	-5.33 ± 1.33			
Median	-4.15	-3.85	-4.8			
Range	-6.3 to -2.5	-4.7 to -3.6	-8.4 to -4.1			

P1: Comparison between **IGHD** and **MPHD** groups
P2: Comparison between IGHD and Turner groups
P3: Comparison between MPHD and Turner groups
IGHD: Isolated Growth Hormone Deficiency
MPHD: Multiple Pituitary Hormonal Deficiency
*** Statistical significance**

Table (3) showed a statistically significant difference between Turner group and each of IGHD and MPHD regarding height velocity, height SDs after 6 months and after 1 year.

Table (4): Change in Height SDs for all Studied Groups

Change in height SDs	IGHD (n= 74)	MPHD (n= 6)	Turner (n= 20)	P1	P2	P3
After 6 months						
Mean ± SD	0.49 ± 0.24	0.48 ± 0.16	0.20 ± 0.11	0.674	0.000**	0.001**
Median	0.40	0.39	0.19			
Range	-0.02 to 1.8	0.13 to 1.23	-0.2 to 0.7			
After 1 year						
Mean ± SD	0.73 ± 0.42	0.83 ± 0.30	0.41 ± 0.21	0.808	0.004**	0.002**
Median	0.72	0.55	0.30			
Range	-0.2 to 2	0.5 to 1.73	-0.2 to 1.4			

P1: Comparison between **IGHD** and **MPHD** groups
P2: Comparison between **IGHD** and **Turner** groups
P3: Comparison between **MPHD** and **Turner** groups
IGHD: Isolated Growth Hormone Deficiency
MPHD: Multiple Pituitary Hormonal Deficiency
** Highly statistical significance

Table (4) showed a statistically significant difference between Turner group and each of IGHD and MPHD regarding change in height SDs after 6 months and after 1 year.

Table (5): Comparison between Height SDs at start, after 6 months and after 1 year of treatment

Groups	IGHD (n= 74)	MPHD (n= 6)	Turner (n= 20)	Significance		
				P1	P2	P3
Height SDs at start of treatment						
Mean ± SD	-4.94 ± 0.98	-4.83 ± 0.52	-5.74 ± 1.40	0.860	0.032*	0.076
Median	-4.78	-4.85	-5.45			
Range	-6.78 to -3.2	-5.33 to -4.3	-8.4 to -4.4			
Height SDs after 6 months of treatment						
Mean ± SD	-4.45 ± 1.00	-4.35 ± 0.50	-5.54 ± 1.31	0.965	0.000*	0.016*
Median	-4.4	-4.1	-5.25			
Range	-6.47 to -2.5	-5.1 to -4.1	-8.2 to -4.2			
Height SDs after 1 year of treatment						
Mean ± SD	-4.21 ± 1.03	-4.00 ± 0.48	-5.33 ± 1.33	0.791	0.000*	0.016*
Median	-4.15	-3.85	-4.8			
Range	-6.3 to -2.5	-4.7 to -3.6	-8.4 to -4.1			
Target height(Cm)						
Mean ± SD	165.41 ± 7.18	173.00 ± 3.70	160.40 ± 2.11	0.030*	0.005*	0.001**
Median	165.5	173.5	160.75			
Range	154.5 to 185	168.5 to 176.5	155.5 to 163.5			

Table (5): showed a statistically significant increase in height SDs6 months and 1 year after treatment compared to height SDs at start of treatment for all groups approaching target height.

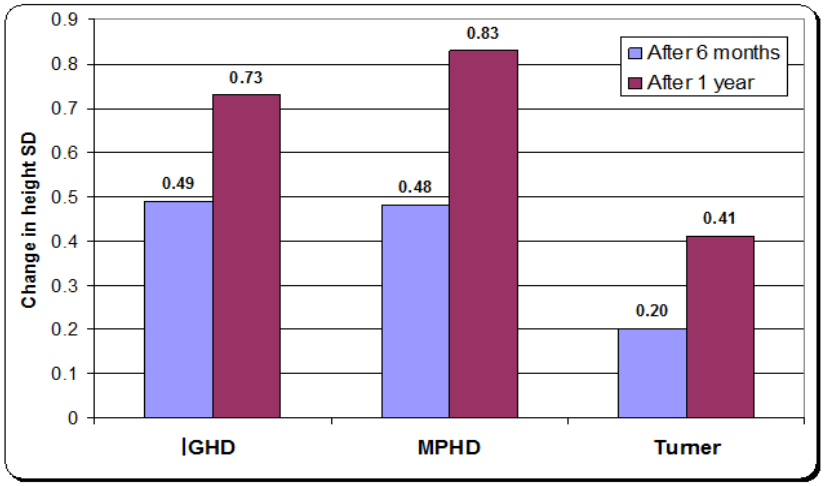

Figure (1): Change in height SDs in total studied groups

Figure (1): showed marked increase in height SDs after 1 year of treatment compared to 6 months after treatment.

Table (6): Correlations between height SDs and different factors affecting it (after 1 year)

Parameters	Change in height SDs after 1 y	
	R	P-value
Chronological age	**-0.302**	**0.001****
Bone age	**-0.403**	**0.000****
Bone age delay	**0.243**	**0.011***
Weight SDs	0.015	0.875
Height SDs	-0.112	0.244
BMI	0.025	0.798
Target height	**0.203**	**0.034***
Growth hormone level	**-0.412**	**0.000****
Change in height SDs after 6 m	**0.793**	**0.000****

Table (6): Showed a statistically significant negative correlation between changes in height SDs after 1 year of treatment and each of chronological age, bone age and GH level. On the other hand a significant

positive correlation were found between changes in height SDs after 1 year and each of bone age delay, target height and change in height SDs after 6 months.

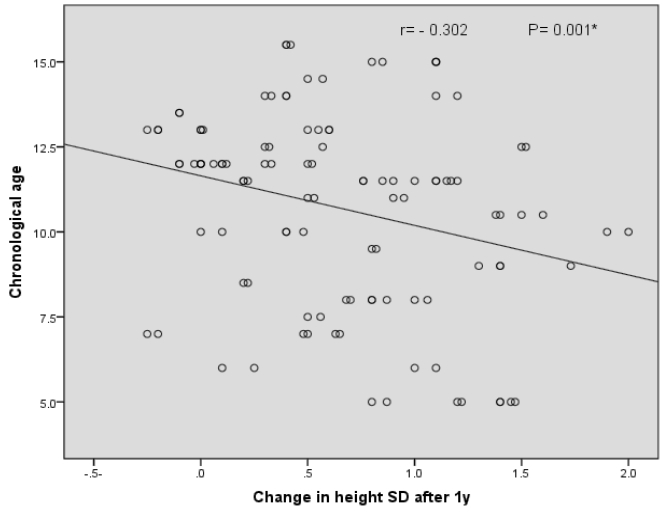

Figure (2): Correlation between change in height SDs after 1 year and chronological age

Figure (2): Showed a statistically significant negative correlation between changes in height SDs after 1 year of treatment and chronological age.

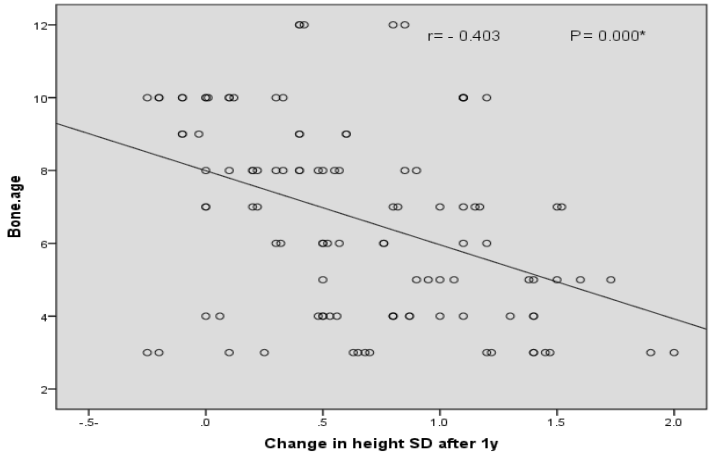

Figure (3): Correlation between change in height SDs after 1 year and bone age

Figure (3): Showed a statistically significant negative correlation between changes in height SDs after 1 year of treatment and bone age.

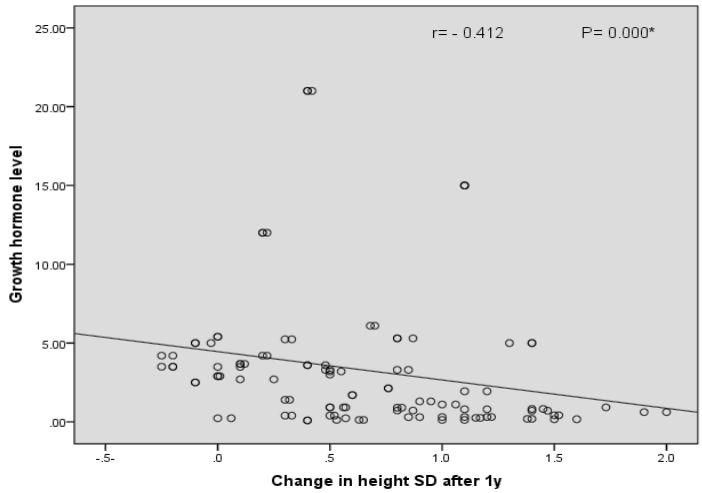

Figure (4): Correlation between change in height SDs after 1 year and growth hormone level at the start of treatment

Figure (4): Showed a statistically significant negative correlation between changes in height SDs after 1 year of treatment and GH level.

DISCUSSION

There was no significant difference between IGHD and MPHD group regard to chronological age, bone age, bone age delay and sex. A Significant difference between IGHD and Turner group regard to chronological age and bone age delay and highly significant difference regard to bone age and sex. There is no significant difference between MPHD and Turner group regard to chronological age with significant difference regard to bone age and bone age delay and highly significant difference regard to sex. Regarding IGHD cases GH therapy let to a good response by increase their height (5-12 cm) during 1st year of treatment. This result was higher than recorded by **(Najala and Ghehad, 2006)** study in which IGHD height increase (5-10 cm) during 1st year. There is highly significant difference in IGHD cases between there height SDs before treatment (-4.94±0.98) and after 1 year of treatment (-4.21±1.03) *P*-value = 0.000, this result in agreement with **(Najala and Ghehad, 2006)** and **(Wit, 2002)**. Regarding cases with MPHD, GH therapy lead to a good response by increase their height (7.5-12 cm) during 1st year of

treatment. The difference between there height SDs before treatment (-4.94±0.98) and after 1 year of treatment (-4.00±0.48) was close to significant *P*-value =0.068, this result in agreement with (**peter et al, 2012).**

Regarding cases with Turner syndrome, GH therapy lead to a good response by increase their height (3.5-8.5 cm) during 1st year of treatment. This result was coordinated with recorded by **(Najala and Ghehad, 2006) and (Ning and Xie, 2000)** studies in which Turner syndrome group height increase (3.5-10 cm) during 1st year. There is highly significant difference in Turner cases between there height SDs before treatment (-5.74±1.4) and after 1 year of treatment (-5.33±1.33), *P*-value= 0.000 this result in agreement with **(Najala and Ghehad, 2006).** As comparing the response of the three study groups to growth hormone therapy after 1 year : The mean change in height SDs in MPHD group(0.83) was higher than IGHD group (0.73), but the difference has no significant *P*-value =0.808 ,but there was significant difference between the two groups in study carried by **(peter et al, 2012) .**

The mean change in height SDs in IGHD group (0.73) was higher than that of Turner group(0.41) with highly significant difference between the two groups *P*-value = 0.004 this result not in agreement with that recorded by **(Najala and Ghehad, 2006)** as they record no significant difference between the two groups.

The mean change in height SDs in MPHD group (0.83) was higher than that of Turner group (0.41) with highly significant difference between the two groups *P*-value =0.002, no reports similar to be compared. As comparing between the response of total study group and 12 year group after 1 year of GH therapy: The mean change in height SDs is higher in (≤ 12 years) group than in total group of IGHD, MPHD and Turner groups that suggest early treatment leading to good response, this result in agreement with (**peter et al, 2012)** and many other studies. In an attempt to determine factors that might have influenced the success of GH therapy we determine the correlation between the change in height SDs after one year of therapy and several parameters *(table 14)* and observe that there is a positive (+ve) correlation coefficient between change in height SDs after 1 year for all study group and bone age delay (r = 0.243), target height (r = 0.203) and change in height SDs after 6 months (r = 0.793).

Negative (-ve) correlation coefficient between change in height SDs after 1 year for all study group and chronological age (r = -0.302), bone age (r= -0.403) and growth hormone level at the start of treatment (r= -0.412). These observations in agreement with the study carried out by **(Bert et al,2013)** , using data from the National Cooperative Growth Study (NCGS) that include pre-pubertal boys and girls with idiopathic GHD, organic GHD ,idiopathic short stature, and Turner syndrome which observe that growth response during first year of treatment largely depend on baseline age also our result come in agreement with **(Ranke et al, 2009)** using data From 4,685 children listed as having ISS within KIGS (Pfizer International Growth Database) which observe –ve correlation between first year growth response and both chronological age, bone age and the more important predictive power can be attributed to bone age delay. other study come in agreement with our study regard to bone age delay carried by **(Wit and Rekers-Mombarg, 2013)** which observe that when bone age delay is relatively great, the effect of GH therapy is relatively good but this study not in agreement with our study regard to the GH peak after provocations as they observe its contribution to outcome parameters in a multiple regression analysis was not statistically significant but in other study carried by **(Paul et al,2013)** observe that younger age has been found to predict better responsiveness to GH, as well as lower peak GH levels in response to provocative testing.

As regard to the positive correlation between change in height SDs and target height observed in our study **(Hochberg and Zadik, 1999)** observe the same result on study carried on 49 young women with Turner syndrome.

Our present study observe no correlation between change in height SD after 1 year for all study group and weight and height SDs at the start of treatment but **(Paul et al, 2013)** observe that the first year growth response is positively correlated to BMI and negatively to baseline height SDs .also **(Nagwa et al, 2015)** observe –ve correlation between first year growth response and baseline weight and height. Other studies also observe other parameters that may influence the success of GH therapy such as GH dosage and serum level of IGF-1 and IGFBP-3.

CONCLUSIONS

Our study showed multiplicity of predictors that is responsible for response to rhGH therapy in patients with short stature. Bone age, chronological age and peak GH level at the start of treatment are important predictor. After one year of rhGH treatment change in height SDs was greater in MPHD and less in Turner group compared with IGHD group, the discrepancy in responses may be due to the disease nature. Increase in height SDs was greatest in children ≤ 12 years old, supporting early treatment initiation to optimize growth outcome.

RECOMMENDATIONS

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(by periodic evaluation of anthropometric measurements even in apparent healthy children). Also we needs to optimize recombinant human growth hormone therapy by individual dose adjustment and this contributes to improved overall outcome specially in girls with Turner syndrome. Further studies on wide scales are needed to evaluate the predictors that is responsible for response to rhGH therapy in patients with short stature.

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الاستجابات المختلفة للعلاج بهرمون النمو في الأطفال الذين يعانون من مرض قصر القامة

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إن التعريف الدقيق لمدى الاستجابة للعلاج بعقار هرمون النمو مازال غير واضح.

وكان الغرض من هذه الدراسة لتقييم مدى الاستجابة للعلاج بهرمون النمو فى الأطفال الذين يعانون من مرض قصر القامة والعوامل التى تؤثر فى ذلك.

هذه الدراسة أجريت على مائة طفل من مناطق مصر المختلفة وذلك فى العيادات الخارجية لمستشفيات التأمين الصحى بأسيوط أربعة وسبعون طفلاً منهم كانوا يعانون من مرض قصر القامة بسبب نقص هرمون النمو فقط وستة أطفال منهم كانوا يعانون من مرض قصر القامة الناتج عن نقص هرمونات الغدة الدرقية عشرون منهم كانوا يعانون من متلازمة ترنر. وكانت تتراوح أعمار الأطفال بين أربع سنوات واثنتا عشرة سنة. وقد تم أخذ التاريخ المرضى للأطفال بعد موافقة ذويهم على إجراء هذه الدراسة ثم فحصهم إكلينيكياً وأخذ قياسات النمو المختلفة لهم (طول ووزن ومحيط للرأس) ووضعهم على منحنيات النمو وكذلك حساب معدل التشتت المعيارى لأطوالهم. وتم عمل الفحوصات المعملية لهم من صورة كاملة للدم وفحص للبول والبراز ووظائف الكبد والكلى وهرمونات الغدة الدرقية وهرمون النمو وتحليل للكروموسومات وعمل أشعة سينية على مفاصل راحة اليد والكوع والكتف لتحديد العمر العظمى. وقد تم إعطاء الجميع هرمون النمو بجرعة 0,6 وحدة دولية لكل كجم فى الأسبوع مقسمة إلى ست جرعات متساوية وتحقن كل جرعة تحت الجلد يومياً ليلاً لمدة ستة أيام فى الأسبوع ويستمر هذا العلاج لمدة عام كامل تتخللها زيارات للمتابعة مرة كل ثلاثة أشهر وذلك لفحصهم وأخذ قياسات النمو لهم.

النتائج: وقد وجدنا استجابة جيدة للعلاج بهرمون النمو فى المجموعات الثلاث حيث كانت الزيادة فى الطول فى المجموعة التى تعانى من نقص هرمون النمو فقط تتراوح بين 5 سم و12 سم خلال العام وكانت هناك فروق ذات دلالة إحصائية بين التشتت المعيارى للطول قبل وبعد العلاج (من 0,98 $\pm$ 4,9 إلى 1,03 $\pm$ 4,2). أما المجموعة التى كانت تعانى من نقص هرمونات الغدة النخامية فكان معدل الزيادة فى الطول يتراوح بين 7,5 سم و12 سم خلال العام وقل التشتت المعيارى لهذه المجموعة من 0,98 $\pm$ 4,9 إلى 0,48 $\pm$ 4 أما المجموعة الأخيرة والتى تعانى من متلازمة ترنر فكان معدل الزيادة فى الطول يتراوح بين 3,5 سم و8,5 سم خلال عام من العلاج وكانت هناك فروق ذات دلالة إحصائية بين معدل التشتت المعيارى قبل وبعد العلاج حيث قل المعدل من 1,4 $\pm$ 5,7 إلى 1,33 $\pm$ 5,3 وتوصلنا إلى وجود علاقة ارتباط موجبة بين التغير فى الطول بعد عام من العلاج وتأخر العمر العظمى والطول المتوقع والتغير فى معدل التشتت المعيارى بعد ستة أشهر من العلاج.