Effect of Human Growth Hormone (HGH) on Children with Achondroplasia (ACH)

A. G. Al-Rawi* MRCP

Mona Abdulghani** FICMS

Abstract:

Back ground: This study, we evaluate the effectiveness of using recombinant GH for ten Achondroplastic children.

Patient & method: the children. (7 females, 3 males) with typical features of achondroplasia, 4-14 years age, participated in this study. Physical and anthropometric measurements were taken every 3 moths, 12 months before and 12 months during GH therapy.

Results: for children less than 10 year of age, the mean growth rate is increased from 3.4±0.4cm/year in the pretreatment period to 8±1.1 cm/year during the first year of GH treatment. For children more than 10 years of age, the mean growth rate is increased from 3.2± 0.6 cm/year in the pretreatment period to 5.6± 1.3 cm/year during the first year of GH treatment.

Conclusion: this study and several other studies confirmed that GH therapy is beneficial in the treatment of short stature in children with Achondroplasia (during the first year of treatment), how ever, is still premature to conclude that the GH will improve the adult height.

Key words: Growth hormone & achondroplasia

Introduction:

Achondroplasia (ACH) is the most common from of chondrodysplasia, its inheritance as an autosomal dominant trait, though most cases are sporadic, recent evidence in molecular biology have revealed its genetic defect in fibroblast growth factor-3 gene. This may introduce a new-diagnostic tools & classification of ACH & related disorders [1, 2, and 3].

ACH is presented at birth with short limbs, a long narrow trunk, a large head with midfacial hypoplastic prominent forehead [4,5,6,7]

ACH is the commonest & best described form of skeletal dysplasias leading to a mean final height of 151 cm+/-5.6 cm for male & 124+/-5.9 cm for female[2,6,7,8,9,10]. The growth velocity is about 3.3 cm/year[10,11,12,13,14].

The head circumference (HC) is obviously enlarged in patient with ACH & special charts for HC are available[2,15,16,17]. Growth hormone has been widely used to treat non GH deficient form of short stature such as Turner's syndrome, skeletal dysplasias, end stage renal failure, intrauterine growth retardation & other beneficial effects, several reports also indicated the short term increase in height velocity among children with Achondroplasia[11.18.19.20].

In this study we evaluated the effectiveness of using recombinant GH therapy for 10 Achondroplastic children.

Patient & Methods:

Ten children (7 females & 3 males) with typical features of Achondroplasia & their ages ranged from 4-14 years old participated in this study.

The diagnosis of ACH was established on the basis of clinical & radiological features, such as large head with prominent forehead, lumbar lordosis & trident hand & radiological findings such as large skull with a relatively small base, decreased lumbosacral interpedicular distance, short pelvis with broad iliac wings & short long bones with wide & flaring metaphyses. Children with atypical feature were excluded (hypochondroplasia). All those children had euthyroidisim & no evidence of spinal cord compression, non-had history of significant neurological or respiratory dysfunction.

The heights of those children were below the 3rd percentile, charts prepared by turner & white House was enrolled in the study. All children have very low growth rate & normal growth hormone levels on conidian stimulant test. Physical examination & anthropometrics measurement were taken every 3 months, 12 months before and 12 months during growth hormone therapy.

The following data were collected by direct interview on both child & his or her family:-

1-name
2-age (date of birth)
3-sex
4-mode of presentation
5-developmental milestone & school performance
6-family history of ACH

Measurement:-

1-Height:-the height was measured with child urged to stretch upwards to the full; and aided in doing so by the measurer applying gentle pressure to his mastoid process, height was measured without shoes or socks. The maximum height was read off to the nearest 0.1 cm. the height measurement was represented by standard percentile range according to growth & development charts for boys & girls prepared by Turner & white house. The measuring instrument was the height / length measuring board & weighing machine used in

this study belongs to CMS weighing equipments Ltd England.

2-The Occipitofrontal circumference was measured by using a tape measure.

Body proportion (the upper/lower body ratio) the lower segment was obtained by measuring the distance between the upper border of the symphysis pubis & the floor in a patient standing against the wall. The upper segment determined by subtracting the lower segment from the standing height.

Growth hormone levels were estimated to all patients using clonidin stimulant test by private laboratories & routine investigations (blood count, urine analysis) and other selective investigations were done when necessary.

X-ray of the hand for bone age determination was performed. Each patient served as her or his own control. The growth rate during the HGH therapy period was compared with that before therapy.

Growth hormone treatment:

Ten patients were treated with recombinant human growth hotmone which was supplied by Serono Pharma S.P.A., Via Casilina 125, Roma, Italy. The growth hormone was administered subcutaneously at a dose of 0.5 U/Kg/Week, 6 days/ week for 1 year.

Result:

Table 1 & figure 1 show the change in growth rate of children with Achondroplasia in the pretreatment & during treatment with growth hormone. Table 2 shows distribution of study sample by age & gender. Figure 2&3 shows the mean of age between under & over 10years of age children with ACH.

Table 1:- Characteristics of study subjects

Age in years	Gender	Age in years	Body height pretreatment	Before treatment	Growth rate(cm/y)	
					During treatment	Changes due to treatment
<10						
1	Female	5.5	85.2	3.4	9.2	5.8
2	Female	6.0	101.1	3.7	6.4	2.7
3	Female	4.7	89.3	3.6	7.6	4.0
4	Male	6.0	106.1	3.6	8.6	5.0
5	Male	4.5	82.2	2.8	8.2	5.4
Mean		**5.3**	**92.8**	**3.4**	**8**	**4.6**
SD		**0.8**	**10.3**	**0.4**	**1.1**	**1.2**
10+						
1	Female	12.0	113.3	3.1	3.9	0.8
2	Female	13.9	123.4	2.3	5.5	3.2
3	Female	11.0	106.2	3.8	7.3	3.5
4	Male	10.0	95.4	3.7	4.7	1.0
5	Male	10.0	109.3	3.2	6.4	3.2
Mean		**11.4**	**109.5**	**3.2**	**5.6**	**2.3**
SD		**1.6**	**10.2**	**0.6**	**1.3**	**1.3**

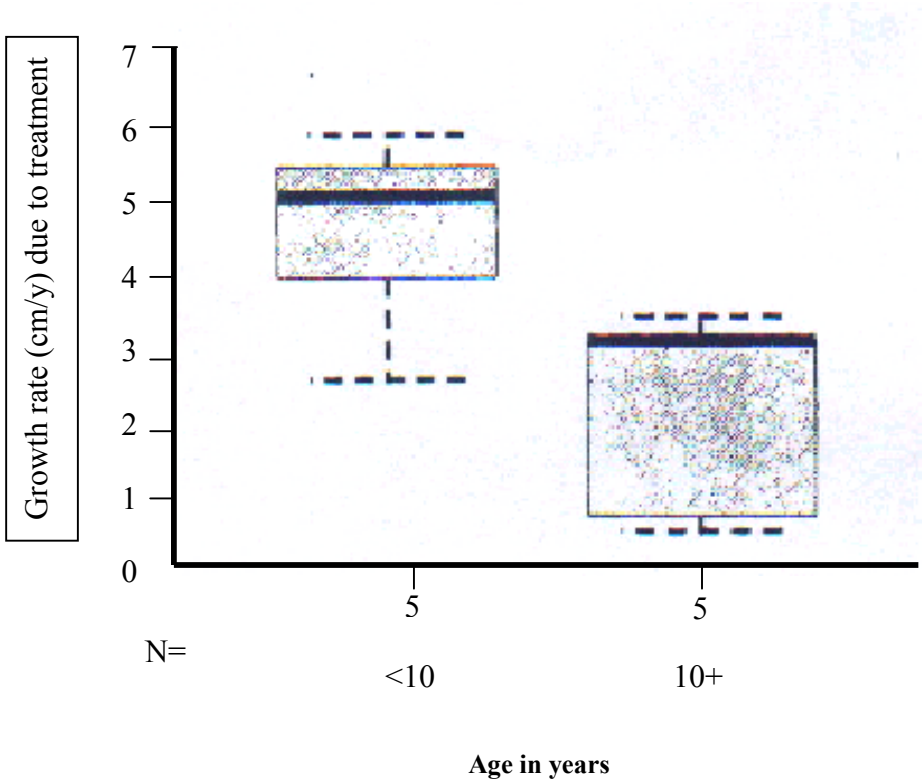


Figure 1: Box plot comparing the distribution of study subject by changes in growth rate due to treatment with GH Achondroplasia children under and over 10 years

Table 2 :- Distribution of the study sample by age and gender.

	N	%
Gender		
Female	7	70.0
Male	3	30.0
Age in years		
<10	5	50.0
10+	5	50.0
Total	**10**	**100.0**

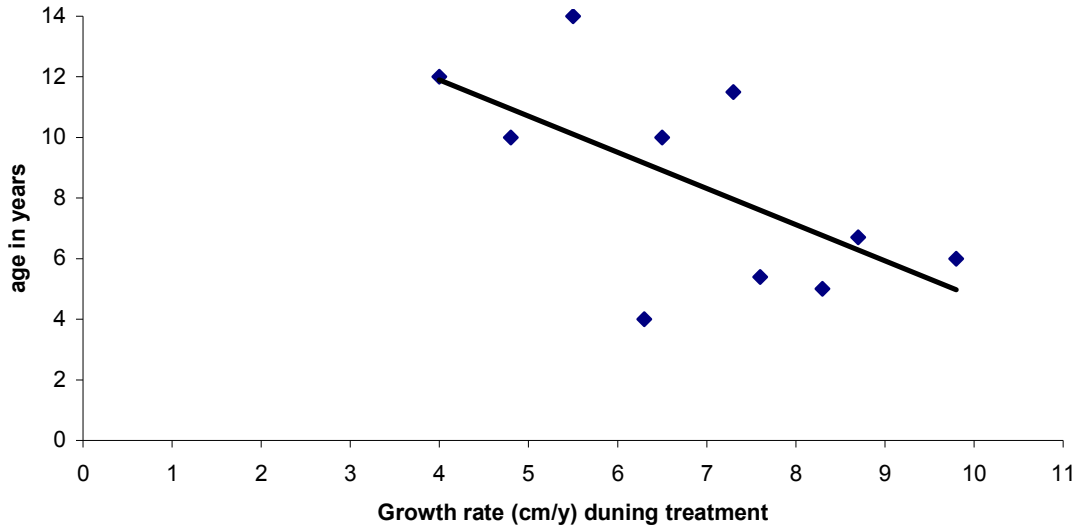


Figure 2: Scatter diagram (with fitted regression line) showing the linear correlation of growth rate during treatment with age in years

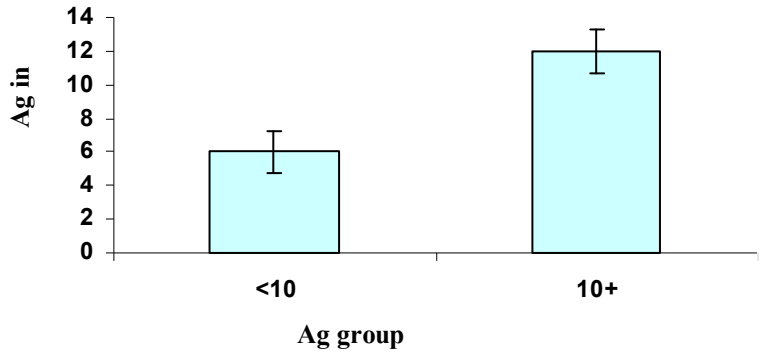


Figure 3: Error bar chart comparing the mean (with its SD) of age between under and over 10 years of age children with Achondroplasia.

For chlidren <10 years of age (group 1) the mean growth rate was increased from 3.4 ±0.4Cm/year in pretreatment period to 8±1.1 cm/year during the treatment. The observed change due to treatment (4.6±1.2 cm/year) was statistically significant (p=0.001 highly significant) as shown in table 3

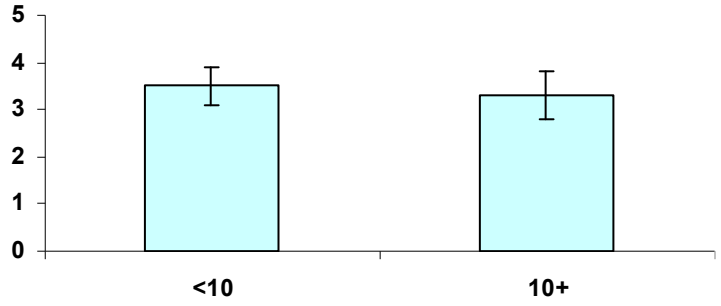
Table 3: The stastical significance of mean change in growth rate due to treatment stratified by age.

Age group	Before treatment	During treatment	Growth rate (cm/y)		P (paired t-test)
			Changes due to treatment	% change (compared to baseline)	
<10 years					
Range	2.8- 3.7	6.4 – 9.2	2.7- 5.8	7.3- 129.9	0.001
Mean	3.4	8	4.6	137.3	
SD	**0.4**	**1.1**	**1.2**	**47.5**	
10= years					
Range	2.3- 3.8	3.9- 7.3	0.8- 3.5	**25.8- 139.1**	0.02
Mean	3.2	5.6	2.3	76.8	
SD	**0.6**	**1.3**	**1.3**	**49.3**	
P(indepndent sample t- test)	**.54 [NS]**	**0.01**	**0.02**		

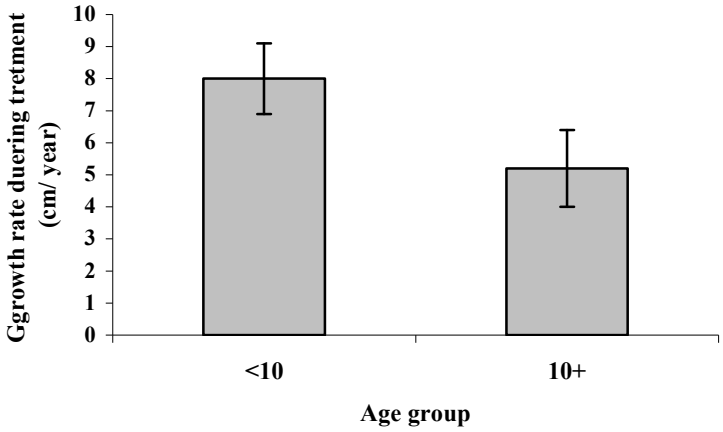
For children >10 years of age group (group2) the mean grwth rate was increased from 3.2±o.6 cm/year in pretreatment period to 5.6± 1.3 cm/yar during the treatment, the observed change due to treatment (2.3 ± 1.3 cm/year) was statistically significant (p=0.02 highly significant) as shown in table 3.

There was no statistically significant difference in the mean growth rate in the pretreatment period between the two age groups (3.4 & 3.2 cm/year) respectively as show in table 3 & figurs 4.

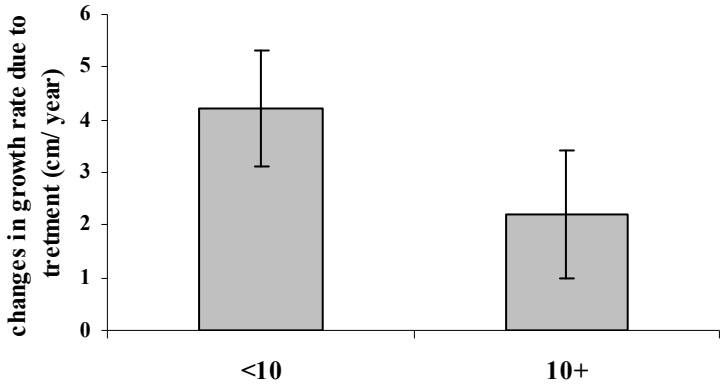
The mean growth rate during treatment was significantly higher among <10 years of age group (8 ±1.1 cm/year) compared to >10 years of age group (5.6 ± 1.3 cm/year) as shown in figure 5. The mean change in growth rate (& percentage change in growth rate) due to treatment was significantly higher among <10 years of age grup (4.6 ± 1.2 cm/year & 173.3%) compared to >10 years of age group (2.3 ± 1.3 cm/year & 76.8%) respectively as shown in figure 6.



Figur 4: Error bar chart comparing the mean (with its SD) of growth rate pretreatment (cm/year) between under and over 10 years of age children with Achondroplasia



Figur 5: Error bar chart comparing the mean (with its SD) of growth rate duing pretreatment (cm/year) between under and over 10 years of age children with Achondroplasia



Figur 6: Error bar chart comparing the mean (with its SD) of change in growth rate due to treatment (cm/year) between under and over 10 years of age children with Achondroplasia

Our data show a linear correlation of growth rate during treatment with age in years as shown in figure 2.

The majority of children have shown significant increase in the growth rate during treatment period 6.62±1.5 cm/year compared to 3.3 cm/year in the pretreatment period. Two females treated with recombinant HGH during the pubertal period did not show significant increase in their growth rate during therapy. One male child age 10 years has shown a growth velocity during treatment less than other two males (ages 4.5& 6 years) but still it is significantly greater than that before treatment 6.4 cm/year compared to 3.2 cm/year as shown in the table 1.

No adverse effects were seen during the treated period.

Discussion :

This study & other similar studies confirm that recombinant HGH doses 0.5u/kg/week increased the 1st year height velocity in patients with Achondroplasia. In this study the mean height velocity increased from 3.3± 1 cm/year to 6.62±1.5 cm/year this finding is higher than the figure reported by Nishi et.al. [19.20.21.22], they reported an increase in height velocity from 3.8±0.7 cm/year to 6±1 cm/year in the 1st year of human growth hormone treatment. The height velocity during the 1st year of GH treatment of patient with 0.5 IU/kg/week used in our study did not differ from those treated at 0.1 IU/kg/week used by other similar study, and also confirmed that one year growth hormone treatment dose not increase body disproportion and has no effect of HGH on head circumference or foramen magnum size [23].

We found that the height velocity of two pubertal females (age 12 & 14 years) was significantly lower than that in a patient during the pre-pubertal stage(figure 6). This finding is similar to those observed by other worker [23]. The precise mechanism of this low responsiveness in the pubertal period is not explained. No untoward effect was observed. A further follow-up study is needed to determine the adult height and probably we have to wait several years.

In conclusion our study and several other studies confirmed that GH therapy is beneficial in the treatment of short stature in children with AGH, however it is still premature to conclude that GH treatment will improve adult height.

References:

1-Tanaka- H. Achondroplsia: Recent advances in diagnosis & treatment. Acta-paediatr-JNP Aug; 39(4):514-2.1997.

2-Kanaka-Gantenbein-C, Present status of the use of growth hormone in short children with bone disease (disease of the skeleton).r J- pediatric-Endocinol Metab. Han 14 (1): 17-26, 2001.

3-Horton WA: fibroblast growth factor receptor 3& the human chondrodysplasia, Nelson textbook of pediatric 699:2120-2123.2000.

4- Nails Thomas hurtle & join Muller. Anthropometric in skeletal dysplasia volume 7, no.2: 155-160.1994.

5- Horton WA. Rotter JI Rimion DL, Scott CI Je, Hall JG standard growth curves for Achondroplasia. J pediatric93:435-438.1978.

6- Tanaer JM, Whitehouse RH, Takashi M. standard from birth to maturity for height & weight velocity : British children part II Arch Dis Chil 41: 613, 1966.

7- Murdoch JL, Walker BA. Hall JC. Abboy Smith KK, Mckusick VA. Achondroplasia genetic & statistical survey. Ann Hum Gen 33:277-244.1970.

8-Wynne Davies R, Walch WK, Gormley J. Achondroplasia & hypoplasia. J Bone Joint Surg 6313:508-515.1981.

9- Walker BA, Murdoch JL, Mckusick VA, Langerlo Beals R K. Hypochondroplasia. Am J Dis Child 122:95-104.1971.

10- Beals RK. Hypochondroplasia. A report of five Kindred J Bone Joint Surg 51A:728-736.1969.

11- M. Shohat, D.Tick, Barakat, X.Bu, S.Melmed S, D.L Rimion: short term recombinant human growth hormone treatment increases growth rate in Achondroplasia. J Chin Endocrionol Metab 81:4033-7.1996.

12-Shiang R, Thompson LM, Zhu Y-Z et.al. 1994 Mutation in the transmembrane domain of FGR3 cause the most genetic from of dwarfism, Forfar: textbook of pediatric, 5th ed: 1575.1998.

13- Paul RM, Scott Wassman ER, JR et.al: Apnea & sudden unexpected death in infants with Achondroplasia. J Pediat 104:342-348. 1984.

14-Spranger J: Radiologic Nosology & bone dysplasia: pediatric approach to skeletal dysplasia. Pediatric annals (v19)2:141-143.1990.

15-Tanaka-H;Kubo-T; Yamata-T;One-T;Kanazaki-S; Seino-Y: Effect of growth hormone therapy in children with Achondroplasia: Growth pattern, hypothalamic-pituitary function, & genotype Eur-J- Endocrinol. Mar; 138(3) :275-280.1998.

16-Horton WA, Hecht JT, Hood Marshal RN, Moor WV & Hollwel JG; Growth hormone therapy in Achondroplasia. American Journal of medical genetics 42:667-670.1992.

17- Horton WA; Approaches to investigation growth plate cartilage in the human chondrodysplasia: Pathol ImmunopthoI Res 72: 85-89.1988.

18-Yamata T, Kanazaki S, Tanaka H et.al: growth hormone treatment in Achondroplasia; J Pediatr Endocrinol.6:45-52.1993.

19- Nishi Y, Kajiyama M,Miyagawa S,Fujiware M, Harmamato K. Growth hormone treatment in Achondroplasia. Acta Endocrinol (Copenh)128:394-396.1993.

20-Kodama H, Okabe I, and Yanajisawa M: Therpeutic benefit of growth hormone treatment in Achondroplasia dwarfism. Acta pediatr Jpn. 32:323-324.1993.

21-Todorov AB, Scott CI, Warren AE, Leeper JD. Devlopmental screening tests in a Hypochondroplasia children. Am J Med Genet 19-23.1981.

22-Daughaday WH: Growth hormone normal synthesis, secretion, control, and mechanisms of action: IN De Groot L(ED): Endocrinology, Philadelphia WH Saunders, 381-329.1989.

23- H.Tanaka etal; Effect of GH therapy in children with Achondroplasia growth pattern, hypothalamic-pituitary function & genotype. European Journal of endocrinology, 138-275.0998.

*From pediatr Dept. Coll. of Med. Al-Mustansiriya Univ.

*From Radiology section Dept Surgery Coll. of Med. Al-Mustansiriya Univ.