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Büyüme Hormon Tedavisi Kemik Yaşını İlerletir mi?

Does Growth Hormone Treatment Advance Bone Age?

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ÖZ

Giriş ve Amaç: Büyüme hormonu (BH) tedavisi, erken epifiz kapanmasına neden olan kemik matürasyonundaki ilerleme konusunda artan endişelerle, kemik matürasyonuna uyarıcı etkide bulunabilir. Bu çalışmada, bu olasılığın araştırılması ve ilerlemiş kemik matürasyonunun tahmini veya son boya etkisinin olup olmadığının saptanmasını amaçladık.

Yöntem ve Gereçler: 1995-2005 tarihleri arasında BH tedavisi alan toplam 230 hastanın verileri retrospektif olarak değerlendirildi. Hastalar; izole BH eksikliği (Grup 1), Turner sendromu (Grup 2) ve diğer (Grup 3) olarak ayrıldı. Önceki el bileği X-ray verileri tıbbi kayıtlardan çıkarıldı ve klinik vizitlerde el bilek X-ray istendi. Kemik yaşı (KY) değerlendirilmesi Greulich ve Pyle atlasına göre yapıldı. Tahmini yetişkin boyu, KY kullanılarak Bayley ve Pinneau metoduna göre yapıldı. Bazal tahmini boy ile tedavinin 1. ve 2. yılındaki tahmini boy, takvim yaş (TY)-KY ve TY/KY değişkenlikleri kullanılarak değerlendirildi.

Bulgular*:* Her üç grupta boy SDS anlamlı olarak arttı ($p<0,05$). Grup 1 ve 2'deki TY-KY, tedavinin 1. ve 2. yılı süresince azaldı ($p<0,05$). KY'ndaki ilerleme, TY/KY oranındaki azalma ile teyit edildi. Bununla beraber, KY ilerlemesine karşın öngörülen boy olumsuz etkilenmedi.

Tartişma ve Sonuç: TY-KY ve TY/KY oranındaki azalma kanıtı olarak BH, KY'nı artırdı. Bununla beraber, tahmini boy iki yıllık tedavi kohortumuzda ilerlemiş kemik matürasyonuna ters olarak etkilenmedi. Bu konu, kemik yaşının daha çok ilerlediği puberte prekoks gibi hasta gruplarında araştırılmalıdır.

Anahtar Kelimeler*:* Büyüme hormon eksikliği, Büyüme hormon tedavisi, Turner sendromu

Türkçe Kısa Başlık*:* Büyüme Hormonu ve Kemik Yaşı

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SUMMARY

***Introduction**:* Growth hormone (GH) treatment may have a stimulatory effect on bone maturation which raises concern about acceleration of bone maturation leading to early epiphyseal fusion. In this study, we aimed to investigate this possibility and determine whether or not accelerated bone maturation affects predicted or final height.

***Methods**:* A total of 230 patients who received GH treatment between 1995 and 2005 were retrospectively studied. The patients were classified as isolated growth hormone deficiency (GHD) (Group-1), Turner syndrome (Group-2), and others (Group-3). The previous X rays were obtained from the medical records and follow-up X rays were requested during the clinic visit. Bone age (BA) assessment was done according to the atlas of Greulich and Pyle. Based on BA, adult height prediction was calculated by the method of Bayley and Pinneau. The predicted height (PH) at baseline and after the first and second years of treatment were evaluated along with the change in chronological age (CA)-BA and CA/BA.

***Results**:* Height SDS significantly increased in all three groups ($p<0.05$). CA-BA decreased in Groups-1 and 2 during the first and second years of treatment ($p<0.05$). The BA acceleration was verified by the decrement in CA/BA ratio. However, predicted height was not negatively influenced despite BA advancement.

***Discussion and Conclusion**:* BA advances with GH treatment as evident from the reduction in CA-BA and CA/BA. However, predicted height is not adversely affected by accelerated bone maturation in our cohort over two years of treatment. This issue needs to be investigated in other patient groups such as precocious puberty where bone maturation is further accelerated.

***Keywords**:* Growth hormone deficiency, Growth hormone treatment, Turner syndrome

***İngilizce Kısa Başlık**:* Growth Hormone and Bone Age

Introduction

Growth retardation due to GHD benefits significantly from GH treatment. Previous reports have indicated concern about acceleration of bone maturation leading to early epiphyseal fusion (1). In contrast, other researchers have demonstrated that high dose compared to low dose GH treatment does not unduly promote the initiation or progression of puberty or bone maturation (2). In this study, we aimed to investigate this possibility and determine whether or not accelerated bone maturation affects predicted or final height.

Material and Methods

*Study Population:*The patients who received GH treatment over a period of two years at Pediatric Endocrinology Department of Uludag University were retrospectively analyzed. The patients who were already on GH therapy when they presented in our clinic were excluded. The patients were classified into three diagnostic groups: Group 1: isolated GHD, Group 2: Turner syndrome, and Group 3: Miscellaneous. GH dose ranged from 0.18 to 0.25 mg/kg/week in Groups 1 and 3, and from 0.30 to 0.45 mg/kg/week in patients with Turner syndrome (Group 2).

*General Description of Data:*The initial diagnostic tests and physical findings, anthropometric measurements, pubertal stage, and GH dose at each visit were recorded from the patient charts. Height was measured with Harpenden ® stadiometer and weight was measured with SEKA ® electronic scale. Height and weight measurements were evaluated with reference to the standards for Turkish children developed by Neyzi et al (3). The previous hand and wrist X rays were obtained from the Radiology Department and follow-up X rays were requested during the clinic visit. BA assessment was done according to the atlas of Greulich and Pyle (4). Based on BA, adult height prediction was calculated by the method of Bayley and Pinneau (5). Clonidine and glucagon stimulation tests were performed and a peak response below 10 ng/ml in both tests was considered as diagnostic for GHD (6,7). Magnetic resonance imaging (MRI) of the pituitary gland was obtained in all patients with GHD.

*Analysis Method:*SPSS 16.0 was utilized for statistical analyses. Shapiro-Wilk test was used to determine whether or not the data demonstrated normal distribution. The difference between the two groups without normal distribution was compared with Mann Whitney U test. Two dependent variables without normal distribution were compared with Wilcoxon Signed ranks test. The data was presented with median, minimum, and maximum values. The level of significance was taken as a=0.05 ($p<0.05$).

Results

Among a total of 246 patients on GH treatment, 230 patients, 131 (57%) male and 99 (43%) female, were included in this study. Sixteen patients were excluded because of noncompliance to therapy. Group 1 (GHD) consisted of 149, Group 2 (Turner syndrome) 34, and Group 3 (miscellaneous) 47 patients. In Group 3, 8 patients had craniopharyngioma, 7 Noonan syndrome, 4 bioinactive GH, 4 achondroplasia, 3 other skeletal dysplasia, 3 APECED syndrome, 2 hypochondroplasia, and 1 Prader Willi syndrome, Klippel Feil syndrome, thalassemia major, osteogenesis imperfecta, postoperative medulloblastoma, primitive neuroectodermal tumor (PNET), Hodgkin's lymphoma, and celiac disease.

The mean peak GH response to clonidine and glucagon tests were 4.58 and 6.01 ng/ml respectively. The mean GH dose was 0.215 (0.15-0.46) mg/kg/week. All three groups responded well to GH treatment (Table 1).

Table1. Mean height SDS before and after GH therapy.

Diagnostic group	Before therapy	After therapy	*P*
Group-1	-3	-2.04	*p<0.05*
Group-2	-3.17	-2.61	*p<0.05*
Group-3	-3.75	-2.82	*p<0.05*

Weight progression was evaluated only in Group 1 because of the possibility of additional factors that may affect nutrition and weight gain in Groups 2 and 3. The relative weight in Group 1 did not differ significantly from baseline at the end of the first (p=0.121) and second (p=0.178) year of GH therapy.

During the first and second year of treatment, the difference between the CA and BA decreased in Groups 1 and 2 (p<0.05). The decrease in Group 3 was significant after the first year (p<0.05), but not so at the end of the second year (p=0,057). The acceleration in bone maturation was also verified by the reduced CA/BA ratio in both treatment years and all three groups (p<0.05) (Table 2).

Table 2. The progression of CA-BA and CA/BA over the two treatment years.

	CA-BA			CA/BA		
Diagnostic groups	Baseline	1st year	2nd year	Baseline	1st year	2nd year
Group 1	3.22	2.66	2.21	1.40	1.26	1.19
p		<0.05	<0.05		<0.05	<0.05
Group 2	1.97	1.85	1.58	1.28	1.22	1.18
p		<0.05	<0.05		<0.05	<0.05
Group 3	2.79	2.29	2.03	1.48	1.30	1.22
p		<0.05	0.057		<0.05	<0.05

In order to investigate the effect of puberty on BA, we separated Group 1 in two subgroups as pubertal and prepubertal. Height SDS increased and CA/BA decreased over both treatment years in both subgroups ($p<0.05$). The two subgroups were not different in terms of height SDS before treatment and the height SDS attained with treatment ($p>0.05$). However, CA/BA was lower in the pubertal group in the beginning, and after the first and second years of treatment ($p<0.05$). In other words, BA was more advanced in the pubertal group at baseline and after the first and second years of treatment as expected (Table 3).

Table 3. The comparison of pre-pubertal and pubertal subgroups of patients with isolated GHD.

	Height SDS			CA/BA		
	Initial	1st year	2nd year	Initial	1st year	2nd year
Prepubertal	-3.00	-2.32	-2.1	1.54	1.31	1.23
p		<0.05	<0.05		<0.05	<0.05
Pubertal	-3.00	-2.42	-1.91	1.25	1.19	1.16
p		<0.05	<0.05		<0.05	<0.05

The PH at the end of the first year of treatment significantly increased in pubertal patients with isolated GHD ($p<0.05$). The PH at the end of the second year of treatment was not significantly different from that at the end of the first year ($p=0.884$). The PH in the prepubertal group increased at the end of the first and second years of treatment, but this did not reach statistical significance probably due to the lower number of patients in this subgroup (Table 4).

Table 4. The comparison of PH (mean $\pm$ SD cm) at baseline and after the first and second years of treatment in prepubertal and pubertal patients with isolated GHD.

	n	Baseline	1st year	2nd year
Prepubertal	60	162.7 $\pm$11,1	165.1 $\pm$10,7	166.8 $\pm$11,9
P			0.52	0.57
Pubertal	89	163.8 $\pm$10,6	165.1$\pm$10,2	166.2 $\pm$11,4
P			<0.05	0.884

Discussion

GHD leads to growth retardation and delay in bone maturation and pubertal development (8). GH treatment not only increases linear growth, but also normalize and may even accelerate pubertal development (9-11). The delayed BA of the patients with GHD become parallel to height age after GH treatment (12). In order to maximize height attainment with GH therapy, linear growth and skeletal development must be proportional (13). However, GH treatment may accelerate bone maturation and it is difficult to quantify the relationship between linear growth and BA progression (11, 12, 14).

In our study, we have demonstrated that the difference between CA and BA decreased after the first and second year of treatment in patient groups 1 and 2. The same trend was observed in Group 3, but the difference did not reach statistical significance during the second year of treatment. BA acceleration was also verified by the reduction in CA/BA ratio in all patient groups after the first and second years of treatment. Radetti et al (15) have reported that high dose GH treatment did not significantly advance BA. Frindik et al (16) have proposed that patients with mildly delayed BA before puberty showed faster BA acceleration during puberty with GH treatment compared to those with more severe BA delay.

Previous studies have shown that GH treatment increases PH without significantly advancing bone (1, 17, 18). Dündar et al (19) have reported that GH treatment increases PH with no significant change in CA/BA ratio. In our study, although BA significantly increased during the first year of treatment, PH also increased significantly among the pubertal patients in Group 1. The PH increased again after the second year of therapy, but this was not statistically significant. The PH in the prepubertal subgroup increased at the end of both treatment years, but this did not reach statistical significance probably due to the lower number of patients in this subgroup. The CA/BA ratio decreased significantly after the first year of treatment in both prepubertal and pubertal groups. However, this acceleration in BA did not impair PH, because PH in both groups increased although statistically insignificant in the prepubertal group and in the second year of pubertal group. These results indicate that bone maturation might have advanced with GH therapy, but this did not deteriorate PH probably due to the concomitant increase in growth rate at least during the two years of GH therapy in this study.

Leschek et al (20) have shown that a GH dose of 0.22 mg/kg/week in 12 year-old boys does not have any affect on the beginning and progression of puberty. In contrast, Cutler et al (21) have reported that a higher dose of 0.5 mg/kg/week in 8 year-old boys and girls has an accelerating affect by one year in the initiation of puberty and progression of BA. These results indicate that the pubertal timing and bone maturation may be affected by GH treatment in a dose-dependent manner. On the other hand, Crowe et al (2) have demonstrated that high dose (0.37 mg/kg/week) compared to low

dose (0.24 mg/kg/week) GH treatment does not unduly promote the initiation or progression of puberty or BA maturation. Since our patients were all on a standard and similar dose of GH, we could not assess the affect of different doses on bone maturation. In our study, we evaluated only Group 1 to compare the prepubertal and pubertal subgroups, because there could be other compounding factors that affect pubertal development in Groups 2 and 3. There was no difference in the height SDS at baseline and the height attainment with therapy between the two subgroups.

In conclusion, we have demonstrated that BA advances with GH treatment as evident from the reduction in CA-BA and CA/BA. However, PH is not adversely affected by accelerated bone maturation in our cohort over the two years of treatment. This issue needs to be investigated in other patient groups such as precocious puberty where bone maturation is further accelerated.

Authors' Contributions

All authors contributed to the work significantly. Enes Salı and Ömer Tarım performed the data analysis and drafted the manuscript. Erdal Eren and Halil Sağlam read and approved the manuscript. Enes Salı was primarily responsible for the conception and design of the study.

Declaration of interest

The authors declare that there are no conflicts of interest in this present study.

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