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ORIGINAL RESEARCH
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Growth hormone treatment in children with idiopathic short stature

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ABSTRACT

Objective: Short stature with no endocrine, metabolic, or systemic problem is defined as idiopathic short stature (ISS). The use of growth hormone (GH) for these children was approved in 2003. The most significant indicator of the treatment's efficacy is the initial response to the treatment. The objective of this study was to examine the factors influencing this response in a particular patient cohort.

Material and Methods: Patients with ISS who started growth hormone and received regular therapy for at least one year were included in the study. Clinical and laboratory findings were retrospectively recorded at the time of admission and at the end of the first year of GH therapy.

Results: A total of 122 patients were included in the study. The mean height SDS improved from -2.74±0.67 to -2.22±0.87 by the end of the first year. The predicted adult height (PAH) increased in 66% of the patients, with a total increase of 1.99±4.1 cm in PAH by one year. The parameters at presentation exhibited no correlation with first-year response parameters such as delta-growth velocity, delta-height SDS, delta-bone age, or delta-PAH.

Conclusion: This study contributes to the field of pediatric endocrinology, providing further insight into the response to growth hormone therapy in a cohort of individuals diagnosed with ISS. The response to GH treatment in ISS is highly variable and influenced by numerous factors. The results highlight the necessity for personalized and precisely targeted management strategies for individuals diagnosed with ISS.

Keywords: Children; growth hormone; idiopathic short stature.

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İdiyopatik boy kısalığı olan çocuklarda büyüme hormonu tedavisi

ÖZET

Amaç: Endokrin, metabolik veya sistemik bir sorun saptanamayan boy kısalığı olgusu "idiyopatik boy kısalığı (İBK)" olarak tanımlanır. Bu çocuklar için büyüme hormonu (BH) kullanımı 2003 yılında onaylanmıştır. Tedavinin etkinliğinin en önemli göstergesi, tedaviye alınan ilk yıl yanıtıdır. Bu spesifik hasta grubunda tedaviye ilk yıl yanıtı ve bunu etkileyen faktörlerle ilişkinin araştırılması hedeflenmiştir.

Gereç ve Yöntemler: Büyüme hormonu başlanan ve en az bir yıl düzenli tedavi alan İBK hastaları çalışmaya dahil edildi. Klinik ve laboratuvar bulguları başvuru anında ve BH tedavisinin ilk yılının sonunda retrospektif olarak kaydedildi. Başvuru parametreleri ile büyüme yanıtı parametreleri arasındaki ilişkiler araştırıldı, başlangıç ve ilk yıl sonu parametreleri karşılaştırıldı.

Bulgular: Çalışmaya toplam 122 hasta dahil edildi. Ortalama boy SDS değeri -2,74±0,67 SDS'den birinci yılın sonunda -2,22±0,87 SDS'ye yükseldi. Öngörülen erişkin boyu (ÖEB), hastaların %66'sında artmış ve bir yıl içinde ÖEB'de toplam 1,99±4,1 cm artış olmuştur. Başvuru sırasındaki parametreler ile delta-büyüme hızı, delta-boy SDS, delta-kemik yaşı veya delta-ÖEB gibi birinci yıl yanıt parametreleri arasında korelasyon saptanmamıştır.

Tartışma: Bu çalışma, İBK tanısı konmuş bireylerden oluşan bir kohortta BH tedavisine alınan yanıt konusunda pediatrik endokrinoloji alanına bir katkı sunmaktadır. Literatürdeki çalışmalara benzer şekilde BH tedavisine yanıtın oldukça değişken ve çok sayıda faktörden etkilendiği düşünülmüştür. Sonuçlar, İBK tanısı konan bireylerde tedavi kararı için bireyselleştirilmiş yaklaşımın gerekliliğini vurgulamaktadır.

Anahtar Kelimeler: Büyüme hormonu; çocuklar; idiyopatik boy kısalığı.

INTRODUCTION

Short stature is defined as a height more than two standard deviations (SDs) below the mean height for a given age and sex in children. It is defined as "idiopathic" when the birth weight is average for gestational age, physical examination and body proportions are normal, systemic diseases are excluded, growth hormone (GH) response to stimulation tests is normal, and an identified cause for short stature is absent. Children with idiopathic short stature (ISS) represent a heterogeneous group with a multitude of non-specific causes of short stature (1). The ISS category also encompasses children with familial short stature and constitutional delay of growth and puberty. In 2003, the United States Food and Drug Administration approved the use of recombinant human growth hormone (rhGH) for children with a height standard deviation score (SDS) of less than -2.25 and a short predicted adult height (2).

The efficacy of growth hormone therapy in this condition has been well acknowledged, where the most significant indicator of the treatment's efficacy is the initial response to the treatment (3). The heterogeneity of responses among patients highlights the complex nature of ISS, emphasizing the urgent need for individualized care pathways and a more comprehensive understanding of the impact of GH therapy on growth parameters in this population (4).

This study represents a contribution to the field of pediatric endocrinology, providing further insight into the response to growth hormone therapy in a cohort of individuals diagnosed with idiopathic short stature. It is anticipated that the comprehensive data collection and analysis will facilitate the generation of valuable results.

MATERIAL AND METHODS

The study population consisted of patients who were initiated on GH therapy for idiopathic short stature at the Pediatric Endocrinology Department between January 1, 2020, and January 1, 2024. The study was approved by the Hospital Ethics Committee (date/number: 27.11.2023/E-54132726-000-230222698) and is in accordance with the Declaration of Helsinki. The clinical and laboratory parameters of the patients were obtained from the medical record systems.

Idiopathic short stature is defined as a condition characterized by short stature in the absence of identifiable endocrine, metabolic, or systemic causes, such as being small for gestational age (SGA), skeletal dysplasia, genetic syndromes, growth hormone deficiency or insensitivity (1). Among patients with normal physical examination findings, normal first-line routine biochemical tests, complete blood count, thyroid hormone levels, and antibody tests for celiac disease, patients with normal IGF-1 and IGFBP-3 levels and a response >7 ng/ml in growth hormone stimulation tests are considered to have idiopathic short stature (1, 5). In our study group, the indication for initiation of GH treatment was a height <-2.25 SDS and short PAH when evaluated with bone age (2).

Male and female patients with short stature younger than 18 years of age who were started on growth hormone therapy and received regular growth hormone therapy for at least one year were included in the study. Patients with any health problem other than idiopathic short stature, those who had interrupted or irregular use of growth hormone in the first year of treatment, those with deficiencies in evaluation parameters, those who developed any systemic disease during follow-up, and those with learning difficulties, eating disorders, or psychosocial problems within the family were excluded from the study.

Clinical findings, anthropometric measurements, laboratory findings, and bone age data were retrospectively recorded at the time of admission and at the end of the first year of growth hormone therapy. The relationships between treatment and

Table 1. Anthropometric parameters of the patients at the start and at the end of one year of the growth hormone treatment

Parameter	At the start of treatment	At one year of treatment	p
Height SDS, n=122	-2.74±0.67	-2.22±0.87	***0.000**[a]
Bone age (years), n=122	9.01±3.02	10.48±2.99	***0.000**[b]
Growth velocity (cm/year), n=47	4.08±1.31	7.95±2.05	***0.000**[c]
Growth velocity SDS, n=47	-1.07±1.16	1.10±1.46	***0.000**[d]
Predicted adult height (cm), n=122	159.1±7.97	161.2±8.73	***0.000**[e]

*: P<0.05 (exact p values: a: 3.693E-14; b: 4.5601E-31; c: 3.5497E-13; d: 0.00004; e: 2.6101E-7). Paired samples T-test. SDS: Standard deviations scores.

change in height standard deviation scores (SDS) and predicted adult height SDS values, age at onset, bone age, birth weight, insulin-like growth factor 1 SDS values, response to growth hormone stimulation tests, and growth hormone starting dose parameters were investigated.

The measurements were conducted with indoor clothes and without having eaten for at least eight hours. The height of each subject was measured without shoes, with the heel, hip, and scapula in contact with the measuring board, and with the head and face in a straight position. The measurements were determined using a height meter with a 1-mm sensitivity and a digital scale with a 100-gram sensitivity. Body weight, height, body mass index, and IGF-1 SDS values were calculated using the CHILD METRICS application, created with references for Turkish children (6, 7).

Statistical Analyses

Data were analyzed using the SPSS 25.0 package program. The distribution of the data was evaluated using the Kolmogorov-Smirnov test. Descriptive statistical methods were employed to evaluate the study data. Data that conformed to a normal distribution were expressed as the mean and standard deviation, while those that did not conform were expressed as the median and interquartile range (IQR). Independent samples t-test was employed for the comparison of normally distributed data between two groups, while the Mann-Whitney U test was used for the comparison of non-normally distributed data between two groups. Pearson correlation analysis was employed for normally distributed data, whereas Spearman correlation analysis was used for non-normally distributed data. Related groups were compared using the paired-samples t-test for normally distributed variables and the 2-related samples (Wilcoxon signed ranks) test for non-normally distributed variables. The significance level was set at p<0.05 for all tests.

RESULTS

A total of 122 patients were included in the study, comprising 57 boys and 65 girls. The mean age of the subjects prior to treatment was 10.9±2.97 years (range 3–16 years), and the mean height SDS was -2.74±0.67 SDS. The dosage of growth hormone treatment was 0.033±0.01. By the end of the first year, the mean height SDS was -2.22±0.87.

Growth velocity data were available for 47 patients, in whom it was 4.08±1.31 cm (-1.07±1.16 SDS) before treatment and increased to 7.95±2.05 cm/year (1.10±1.46 SDS) at the end of the first year under GH treatment. The mean height gain in the first year of treatment in the entire study group was 8.64±2.68 cm (0.47±0.72 SDS) (Table 1).

Correlation analyses were conducted to investigate potential associations between the study parameters. The results indicated that delta-PAH was positively correlated with delta-height (r=0.176; p=0.053) and delta-height SDS (r=0.194; p=0.044), while it was negatively correlated with bone age under treatment and delta-bone age at one year of the treatment (r=-0.252; p=0.005 and r=-0.608; p=0.000, respectively). The delta-bone age parameter did not exhibit a correlation with BMI SDS, growth hormone dose, or mid-parental height. The parameters at presentation (age, bone age, birth weight, IGF-1 levels, and growth hormone responses in two stimulation tests) also exhibited no correlation with first-year response parameters such as delta-growth velocity, delta-height SDS, delta-bone age, or delta-PAH.

When patients were evaluated individually, PAH increased in 66% of the patients at the end of the first year, with a total increase of 1.99±4.1 cm in comparison to the pretreatment value. However, 33% of the patients exhibited a lower PAH, which was likely attributable to acceleration in bone maturation as well as growth velocity. An increase in PAH was considered a good response, and good responders were compared with poor responders. The age at presentation, gender, birth weight, bone age, delta-bone age at one year, weight SDS, BMI SDS, target height, IGF-1 levels, GH responses in the stimulation tests, and GH dose were not significantly different between good and poor responders.

DISCUSSION

The clinical definition of idiopathic short stature is based on the exclusion of other causes and demonstrates a highly heterogeneous distribution within itself. While current literature includes constitutional and familial short stature cases under this heading, our study focused exclusively on patients undergoing GH treatment who are expected not to reach their target height (2, 8, 9). Nevertheless, it remains challenging to differentiate between physiological short stature and this group

with certainty. The remarkably high growth rate observed in some patients may potentially be attributed to the influence of growth hormone on the pubertal growth spurt. Consequently, the response to treatment exhibits variability, as evidenced by the considerable range in growth rates and PAH parameters observed at the end of the first year in some of our patients. As a result of our study, although there was a significant increase in growth parameters in the first year of treatment, only a limited increase in total predicted adult height could be achieved.

The first-year response to GH therapy for idiopathic short stature showed varying degrees of improvement in growth parameters, with a mean increase in height SDS of 0.47±0.72, indicating a favorable response to the treatment modality. Statistically significant changes in height SDS and PAH indicate a favorable outcome for a significant proportion of patients. However, the response across the cohort was highly variable, reflecting the multifaceted nature of this condition. In a consensus statement produced by the Pediatric Endocrine Society, the Growth Hormone Research Study, and the European Society for Pediatric Endocrinology, an adequate response was defined as an increase in height SDS of at least 0.3–0.5 SDS within the first year of rhGH initiation (10). Results in the meta-analysis from the Cochrane database report suggest that short-term height gains can range from none to approximately 0.7 SDS over one year (11). Data from KIGS, the largest and longest-running international database of GH-treated children, show that the median first-year delta-height SDS was 0.66 in prepubertal ISS patients (12).

A significant correlation was observed between the change in PAH and height SDS after the first year of treatment, suggesting a concordant relationship between improvements in PAH and the observed increase in height SDS. This finding highlights the potential predictive value of growth parameters during the treatment course for final height and emphasizes the importance of these measurements in prognosis and further treatment planning for patients with ISS.

The results indicated that, as expected, delta-PAH was positively correlated with delta-height, while it was negatively correlated with the advance in bone age under treatment. The increase in height SDS values and growth velocity under treatment did not correlate with baseline age, gender, bone age, IGF-1 levels, or growth hormone levels. The delta-bone age parameter also did not exhibit a correlation with BMI SDS, growth hormone dose, mid-parental height, age, bone age at presentation, birth weight, IGF-1 levels, or growth hormone levels. The lack of significant correlations between treatment responses and these parameters indicates that ISS is a multifactorial condition. This lack of clear associations emphasizes the complex and multifaceted nature of the condition (13–17).

At the end of one year, PAH increased in 66% of the patients compared to the baseline evaluation. However, 33% of the patients exhibited a lower PAH, likely attributable to acceleration in bone maturation as well as growth velocity. Since the delta-bone age parameter was not correlated with growth parameters or GH dose, it was thought that the acceleration in bone maturation was due to puberty, which may vary individually, rather than growth hormone treatment. A study from Korea showed height improvement and mild bone age acceleration over the first three years of GH treatment (18). Another study from our country, conducted by Şıklar et al., (19) emphasized the safety and efficacy of GH treatment in ISS; however, similar to our study, their study group also included prepubertal and pubertal subjects. When they compared poor responders with good responders, nutritional status and target height were the remarkable factors affecting height gain.

A poor response should prompt the treating physician to take action. This could involve modifying the therapy or reviewing the primary diagnosis, which could result in either discontinuing or changing the therapy. The prevention of a poor response is addressed by discussing strategies for first-year management. Adherence to therapy is also a key issue (20).

The findings of our study indicated that the response to GH treatment in ISS is highly variable and influenced by numerous factors. However, we were unable to identify a predictive factor at the start of treatment. The observed complex and heterogeneous responses highlight the necessity for personalized and precisely targeted management strategies for individuals diagnosed with ISS.

Ethics Committee Approval: The Istanbul Health Sciences University Ümraniye Training and Research Hospital Clinical Research Ethics Committee granted approval for this study (date: 27.11.2023, number: E-54132726-000-230222698).

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