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ORIGINAL RESEARCH
Pediatric Endocrinology

Isolated growth hormone deficiency and combined pituitary hormone deficiency in children: Clinical features and response to treatment

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ABSTRACT

Objective: Congenital hypopituitarism is generally due to genetic disorders in children. Variants in genes expressed during the earliest stages of embryologic development are usually associated with multiple hormone deficiencies, whereas variants in genes involved in later stages of pituitary development result in more specific hormone deficiencies.

Material and Methods: The clinical features and treatment responses of patients with isolated growth hormone deficiency (GHD) and combined pituitary hormone deficiency (CPHD) were investigated. Isolated GHD was defined as an inadequate response to two growth hormone stimulation tests (<5 ng/ml); CPHD was defined as GHD accompanied by one or more additional pituitary hormone deficiencies. Patients receiving GH treatment due to idiopathic short stature (ISS) with a GH level >7 ng/ml were assigned as the control group.

Results: Fifty-seven patients with GHD (44 with isolated GHD, 13 with CPHD) and 122 controls with ISS were included. First-year height gain was higher in both isolated GHD and CPHD patients compared to controls (p=0.017, p=0.036, p=0.036, p=0.000, p=0.000, p=0.000, respectively), more prominently in the CPHD group. This increase was 0.7 SDS in those with isolated GHD and 1.3 SDS in those with CPHD.

Conclusion: In patients with GHD, a younger age at treatment initiation, a younger bone age, and lower initial GH levels in stimulation tests are associated with a more pronounced response during the first year of treatment. CPHD was associated with more severe deficiency compared to isolated cases, and other anterior pituitary hormone deficiencies did not adversely affect the response to treatment.

Keywords: Combined pituitary hormone deficiency; growth hormone therapy; idiopathic short stature; isolated growth hormone deficiency.

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Çocuklarda izole büyüme hormonu eksikliği ve çoklu hipofiz hormon eksikliği: Klinik özellikler ve tedaviye yanıt

ÖZET

Amaç: Konjenital hipopitüitarizm, çocuklarda genellikle genetik bozukluklara bağlıdır. Embriyolojik yaşamın en erken evrelerinde rol alan genlerdeki varyantlar genellikle çoklu hormon eksiklikleriyle ilişkiliyken, hipofiz gelişiminin daha sonraki evrelerinde etkili olan genlerdeki varyantlar daha spesifik hormon eksikliklerine neden olur.

Gereç ve Yöntemler: İzole büyüme hormonu eksikliği (BHE) ve çoklu hipofiz hormonu eksikliği (ÇHHE) olan hastaların klinik özellikleri ve tedaviye yanıtları araştırıldı. İzole BHE, iki büyüme hormonu uyarı testine yetersiz yanıt veren (<5 ng/ml) olgular olarak tanımlandı; BHE'ye bir veya daha fazla ek hipofiz hormonu eksikliğinin eşlik ettiği olgular ise ÇHHE olarak tanımlandı. İdiyopatik boy kısalığı (İBK) nedeniyle büyüme hormonu (GH) tedavisi alan ve GH düzeyi >7 ng/ml olan hastalar kontrol grubu olarak belirlendi.

Bulgular: Büyüme hormonu eksikliği olan 57 hasta (44 izole, 13 çoklu hipofiz hormon eksikliği) ve 122 İBK olgusu kontrol grubu olarak çalışmaya dahil edildi. Birinci yıl boy uzaması hem izole BHE hem de ÇHHE hastalarında, ÇHHE olanlarda daha belirgin olmak üzere, kontrol grubuna kıyasla daha yüksekti (sırasıyla p=0,017, p=0,036, p=0,036, p=0,000, p=0,000, p=0,000). Bu artış izole BHE olanlarda 0,7 SDS, ÇHHE olanlarda ise 1,3 SDS idi.

Tartışma: Tedaviye başlama yaşının daha küçük, kemik yaşının daha genç ve uyarı testlerinde büyüme hormonu yanıtının daha düşük olması, tedavinin ilk yılında daha belirgin bir yanıtla ilişkili bulunmuştur. Büyüme hormonu düzeyleri ÇHHE olgularında izole vakalara kıyasla daha ciddi olarak eksiktir ve tedaviye yanıt daha iyi olup, diğer ön hipofiz hormonu eksikliklerinin tedavi yanıtını olumsuz etkilemediği sonucuna varılmıştır.

Anahtar Kelimeler: Büyüme hormonu tedavisi; Çoklu hipofiz hormon eksikliği; İdiyopatik boy kısalığı; İzole büyüme hormonu eksikliği.

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INTRODUCTION

Growth hormone deficiency (GHD) is the most common endocrine cause of growth retardation, which is either isolated or a component of "combined pituitary hormone deficiency (CPHD)" due to genetic or acquired disorders. Congenital hypopituitarism is generally due to genetic disorders in children. The molecular mechanisms underlying fetal hypothalamic and pituitary development may explain the pathophysiology of congenital hypopituitarism. Variants in the genes expressed in the earliest stages of embryologic life are usually associated with syndromic forms, usually with multiple hormone deficiencies, while variants in genes involved in later stages of pituitary development result in non-syndromic forms with more specific hormone deficiencies. Autosomal recessive, dominant, or X-linked inherited variants in these early-stage genes lead to dysgenetic development of the hypothalamus and pituitary gland, resulting in syndromes such as septo-optic dysplasia, holoprosencephaly, pituitary stalk interruption, and CHARGE syndrome, while variants in PROP1 and POUF1F1 result in non-syndromic multiple pituitary hormone deficiency (1). Variants in GHRHR (growth hormone-releasing hormone receptor), GHSR (growth hormone secretagogue receptor), and GH1 (growth hormone gene) are associated with isolated GHD. Isolated GHD has an incidence of 1:4,000 to 1:10,000 live births (2).

Recombinant human growth hormone (GH) is used in the treatment of short stature resulting from GHD. Pediatric indications for treatment also include Turner syndrome, Prader-Willi syndrome, small for gestational age, chronic renal insufficiency, and idiopathic short stature. As the indications expanded, the effectiveness and cost-benefit relationship of GH treatment, which has become widespread, became more debated. The outcomes of GH treatment given for various indications started to be published more and more in the literature (3, 4).

Growth hormone stimulation tests are essential tools for diagnosing GHD. Pharmacologic agents to stimulate GH secretion, such as clonidine, L-dopa, arginine, or glucagon, are used. Failure to respond to two provocative stimuli is needed to diagnose GHD; however, assay-specific cutoffs are required to define GHD. Recent studies using newer assays suggest a GH response of >7 mcg/L to exclude GHD, and <5 mcg/L to diagnose definite GHD. It is also highlighted in studies that severe GHD, defined as a peak GH level of <3 mcg/L, is associated with better growth catch-up with even lower GH doses (5–7).

In this study, we evaluated the clinical features and treatment responses of isolated GHD and CPHD patients who received growth hormone therapy in a single pediatric endocrine center.

Table 1. Clinical characteristics of patients with growth hormone deficiency and idiopathic short stature at presentation and during growth hormone therapy

Clinical feature	Growth hormone deficiency	Idiopathic short stature	p
Age (years)	10 (5.9)	12 (4.2)	0.003*
Puberty (+/-)	17 / 40	34 / 88	0.787
Weight SDS	-1.50 (2.18)	-2.32 (1.46)	0.001*
Height SDS	-2.70 (1.15)	-2.57 (0.86)	0.447
BMI SDS	0.00 (2.20)	-0.87 (1.52)	0.000*
IGF-1 SDS	-1.95 (0.80)	-1.14 (1.10)	0.000*
First year GH dose (mg/kg/d)	0.031 (0.002)	0.033 (0.005)	0.002*
First year height SDS	-2.10 (1.10)	-2.20 (0.87)	0.213
First year height gain (cm)	9.2 (4.0)	8.5 (3.2)	0.000*
First year height SDS increase	0.75 (0.55)	0.41 (0.85)	0.001*

*: P<0.05; BMI: Body mass index; GH: Growth hormone; IGF-1: Insulin like growth factor-1; SDS: Standart deviation score.

MATERIAL AND METHODS

Patients who were started on GH treatment due to GHD in our clinic were included in the study. The study group was assigned into two groups as "isolated GHD (growth hormone deficiency)" and "CPHD (combined pituitary hormone deficiency)". Isolated GHD was defined as cases with pre-treatment height <-2 SDS, inadequate growth rate, and inadequate response to two growth hormone stimulation tests (<5 ng/ml); CPHD was defined as cases with pre-treatment height <-2 SDS, inadequate growth rate, and inadequate response to two growth hormone stimulation tests (<5 ng/ml) accompanied by one or more additional pituitary hormone deficiency. Patients receiving GH treatment due to idiopathic short stature (with a GH level of >7 ng/ml) were assigned as the control group. The study was approved by the Hospital Ethics Committee (date/number: 23.11.2023/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.

Patients with short stature younger than 18 years of age who were started on GH and received regular 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 were excluded from the study.

Clinical findings, anthropometric measurements, laboratory findings, and bone age data were retrospectively recorded at presentation and at the end of the first year of growth hormone therapy. The measurements were made using a height meter with 1-mm sensitivity and a digital scale with 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 (L, M). Clinical and laboratory parameters were compared between definite GHD patients and ISS patients, followed by comparisons between isolated GHD and CPHD groups. The correlations between "change in height standard deviation scores (SDS)" and "predicted adult height SDS", "calendar age and bone age at presentation", "birth weight", "insulin-like growth factor-1 (IGF-1) SDS at the beginning of treatment", "stimulated GH levels" and "GH dose" were investigated.

Statistical Analysis

The SPSS 25.0 package program was used for analyses. The distribution of the data was evaluated using the Kolmogorov-Smirnov test. Descriptive statistical methods were employed to evaluate the study data. Since data did not show normal distribution, results were expressed as the median and interquartile range (IQR). Mann-Whitney U test was used for the comparison between two groups. Spearman correlation test was used for correlations for non-normally distributed data. The significance level was set at $p<0.05$ for all tests.

RESULTS

Of the 57 patients in the study group, 44 had isolated GHD and 13 had CPHD. There were 122 patients receiving GH due to idiopathic short stature (ISS) in the control group. The mean age of the study group was 10.4±3.3 years, and 71.5% were in the prepubertal stage. The median height before treatment was -2.70 in the study group and -2.57 in the ISS group, and was statistically similar. At the end of the first year, there was an increase of 0.75 SDS in the study group and 0.41 SDS in the ISS group (p=0.001). The clinical features of the growth hormone-deficient group and the control group at presentation and under growth hormone treatment are shown in Table 1.

Table 2. Clinical characteristics of patients with isolated growth hormone deficiency and combined pituitary hormone deficiency at presentation and during growth hormone therapy

Clinical feature	Isolated growth hormone deficiency	Combined pituitary hormone deficiency	p
Age (years)	10.5 (5.5)	6.0 (5.0)	0.001*
Weight SDS	-1.40 (2.0)	-1.8 (3.9)	0.441
Height SDS	-2.80 (1.10)	-2.30 (2.3)	0.909
BMI SDS	0.13 (2.19)	-0.08 (2.89)	0.711
IGF-1 SDS	-1.80 (0.7)	-2.60 (0.4)	0.001*
GH response (clonidin)	2.70 (2.5)	0.80 (1.5)	0.001*
GH response (glucagon)	3.0 (2.6)	1.20 (2.2)	0.001*
First year GH dose (mg/kg/d)	0.031 (0.002)	0.030 (0.006)	0.351
First year height SDS	-2.20 (0.90)	-1.50 (1.95)	0.331
First year height gain (cm)	9.0 (3.0)	12.0 (3.0)	0.009*
First year height SDS increase	0.70 (0.48)	1.30 (0.85)	0.001*

*: P<0.05; BMI: Body mass index; GH: Growth hormone; IGF-1: Insulin like growth factor-1; SDS: Standart deviation score.

First-year height gain and height SDS increase were higher in both isolated GHD and CPHD patients compared to controls (p=0.017, p=0.036, p=0.036, p=0.000, p=0.000, p=0.000, respectively), more prominently in the CPHD group. This increase was 0.7 SDS in those with isolated GHD and 1.3 SDS in those with CPHD. Age at diagnosis, pre-treatment IGF-1, and stimulated GH levels in both tests were significantly lower in CPHD patients compared to isolated GHD patients (p=0.001, p=0.001, p=0.001, p=0.001, p=0.001, p=0.002, respectively). The increase in height in the CPHD group was 0.6 SDS higher than in the isolated GHD group (12 cm versus 9 cm) with one-year treatment (p=0.002). The comparison of the findings of isolated GHD and CPHD cases at presentation and under growth hormone treatment is shown in Table 2.

In the study group, first-year height gain was negatively correlated with “age at the beginning of treatment”, “bone age”, “IGFBP-3”, and “peak GH level in stimulation tests”.

DISCUSSION

The findings of this study indicated that the response to GH treatment was predominantly associated with the severity of growth hormone deficiency, being more severe in patients with CPHD compared to those with isolated conditions. In patients diagnosed with GHD, a younger age at treatment initiation, a younger bone age, and lower initial GH levels in stimulation tests are associated with a more pronounced response during the first year of treatment.

In this study, SDS values were used in anthropometric measurements and calculations because the study group and controls differed in mean age. There was no difference in terms of presence of puberty and initial height SDS between GHD and ISS patients. Weight and BMI values were significantly higher in GHD patients compared to ISS patients. In fact, inadequate linear growth is an important feature that is taken into consideration in the clinical evaluation of patients with GHD despite normal or high weight and absence of nutritional deficiency. Children with GHD have an altered body composition and metabolic profile, lower bone mineral density, delayed skeletal maturation, and increased percentage of body fat with central fat deposition, and accompanying lean mass reduction (8).

The lower the level detected in the tests, the better the response to treatment, as shown by the negative correlation between the “first-year height SDS gain” parameter and age, bone age, IGFBP-3, and peak GH level in stimulation tests in our study results. In an interesting study by Lanzetta et al. (9), 153 patients with short stature and pathological response to two GH stimulation tests were investigated. Patients with definite GHD were defined as those with a clear genetic or anatomical hypothalamic-pituitary anomaly, and CPHD. Others were defined as “short stature unresponsive to stimulation tests.” IGF-1 SDS was significantly lower in definite GHD. After one year of treatment, height gain was not different between groups, while the increase in IGF-1 SDS was greater in the definite GHD group, closing the gap. When patients reached near adult height, they underwent retesting for GHD. The prevalence of pathological retesting was higher in definite GHD, as well as the prevalence of overweight and obesity.

In our study group, patients with CPHD had presented at a significantly earlier age than those with isolated GHD. There was no significant difference between anthropometric measurements and SDS values. However, IGF-1 SDS values and GH peak responses were significantly lower in those with CPHD, and first-year responses to treatment were significantly higher. Although there was no significant difference in clinical severity except for age at presentation, the more dramatic response to treatment in those with CPHD showed that biochemical severity is very helpful in predicting treatment response. Similar to ours,

the study by Donbaloğlu et al. (10) showed that the lower the GH peak in provocation tests, the better the response to treatment. The best height velocity was observed in the first year of rhGH therapy. They argue that the diagnosis should be checked in patients who had a low first-year response and did not have a severely low GH peak in provocation tests.

Long-term responses beyond the first-year response may be more variable. Lim et al. (4) showed that 3-year GH treatment was effective in both idiopathic and organic GHD patients regardless of the presence of CPHD or underlying causes. Maghnie et al. (11) investigated 39 patients with isolated GHD and 49 patients with CPHD and reported that the adult height in patients with permanent isolated GHD and spontaneous puberty is similar to adult height in patients with CPHD and induced puberty.

CONCLUSION

In conclusion, the results of our study showed that better height gain with GH in patients with CPHD was associated with more severe deficiency compared to isolated cases, and that other anterior pituitary hormone deficiencies do not adversely affect the response to treatment if adequately treated.

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

Informed Consent: Written informed consent was obtained from the families of the patients who participated in this study.

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