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An evaluation of IGF-1 and IGFBP-3 levels in patients receiving growth hormone therapy and these parameters therapeutic efficacy

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Abstract

Serum insulin-like growth factor-1 (IGF-1) and insulin-like growth factor-binding protein-3 (IGFBP-3) levels in healthy children reflect endogenous growth hormone (GH) levels, and their daily variations are very low. This study investigated the relationship between growth response and serum IGF-1 and IGFBP-3 levels before and on the first year of treatment in children with GH deficiency (GHD) started on GH therapy. The records of 44 patients diagnosed with GHD, under follow-up at the Adıyaman Education and Research Hospital Pediatric Endocrinology Clinic, and receiving GH therapy for at least one year were examined retrospectively. Patients' ages, pubertal development stages, peak GH-responses to GH stimulation tests and height standard deviation scores (SDS) measured before and at the first year of treatment, and IGF-1 and IGFBP-3 levels were recorded. Girls represented 27 (61.4%) of the cases in the study and boys 17 (3.6%), with ages ranging between 0.5 and 16.6 years (mean=11.5±3.3). Partial GHD was present in 33 patients (75%) and complete GHD in 11 (25%). Basal height SDS, IGF-1 and IGFBP-3 values were compared with those after one year of treatment. Patients with basal IGF-1 levels < -2 SDS exhibited significantly higher growth responses ($p < .05$). All three parameters' mean values were significantly higher after one year compared to baseline. Δ IGF-1 and Δ IGFBP-3 values investigated in the first year of treatment together with basal IGF-1 levels can be a useful diagnostic tool in showing growth response in children with GHD started on GH therapy.

Keywords: growth hormone, growth hormone therapy, insulin-like growth factor-1, insulin-like growth factor-binding protein-3

1. Introduction

Growth hormone deficiency (GHD) is a severe endocrine disorder leading to short stature and is seen in approximately one in 4000 live births (1). Since growth hormone (GH) release exhibits diurnal variation, basal GH level measurement is not meaningful in diagnosing GHD. GH stimulation tests are therefore needed in cases requiring GH level investigation (2).

Insulin-like growth factors (IGFs) are GH-dependent peptide factors that mediate the effects of GHs (3). In healthy children, serum IGF-1 and insulin-like growth factor-binding protein-3 (IGFBP-3) levels reflect endogenous GH secretion. Diurnal variations in IGF-1 and IGFBP-3 levels are insignificant (4). Therefore, both serum IGF-1 and IGFBP-3 levels have been reported to be capable of use as screening tests in diagnosing GHD (5, 6).

Prompt diagnosis and early commencement of treatment of GHD are of great importance in children's reaching target heights (5, 7, 8). Patients started on GH therapy must be followed up in terms of efficacy (9). Growth velocity and IGF-1 and IGFBP-3 levels can be evaluated in terms of the effectiveness of treatment in these cases (10).

This study aimed to investigate the relationship between growth response and serum IGF-1 and IGFBP-3 levels before and during the first year of treatment in children with GHD who started GH therapy.

2. Materials and Methods

2.1. Study design

This study was performed using data from 44 patients followed up with diagnoses of GHD at the Adıyaman University Education and Research Hospital Pediatric Endocrinology Clinic, Turkey, between August 2016 and February 2021 and receiving GH therapy for at least one year. We took approval for the study from the Adıyaman University Non-Interventional Research Ethical Committee (decision no. 2020/7-7 dated 21/07/2021). We recorded the patients' ages, pubertal development stages, height standard deviation scores (SDS), basal IGF-1 SDS, basal IGFBP-3 SDS, and peak GH response values to clonidine and L-Dopa stimulation tests. Inclusion criteria were the following: 1) The patient's height at the time of presentation <-2 Standard

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Deviation Score (SDS) for age and gender or <3rd percentile, 2) annual growth velocity <25th percentile, 3) bone age two years or more behind calendar age in prepubertal children, 4) exclusion of pathological causes of short stature other than GHD, such as systemic diseases, Turner syndrome, and skeletal dysplasias, and 5) an insufficient GH response to at least two GH stimulation tests (peak GH response to GH stimulation test <10 ng/mL) (11,12). We divided the patients into two groups based on the maximum GH response to the clonidine and L-Dopa GH stimulation tests, partial GHD (stimulated maximum GH response 5.1-10 ng/ml) and complete GHD (stimulated maximum GH response ≤ 5 ng/ml). We calculated the difference (Δ) in the laboratory and clinical data investigated before and one year after commencement of GH therapy as the change in the two values. We further divided the patients into two groups: Those with basal IGF-1 and IGFBP-3 levels deviating less than -2 Standard Deviation (SD) and those with deviations more than -2 SD. We calculated IGF-1 and IGFBP-3 SDS values based on age- and gender-specific reference values for healthy Turkish children (13).

We excluded patients with regular follow-up times of less than one year, those who started GH therapy in another center, those not adhering to GH therapy, or those with incomplete data in the patient files.

A children's nurse working in the pediatric endocrine clinic measured the heights of patients under two years in the supine position and those over two years standing barefoot, with their heads erect, hips and shoulders against a wall, and heels together. Measurements were taken using a SECA 216 stadiometer with 1 mm graduations. We calculated the target height of the patient's using the formula (father's height -13 + mother's height) / 2 for girls and (father's height + mother's height +13) / 2 for boys. We calculated estimated adult heights using the Bayley-Pinneau method (15). We determined the pubertal stages of the patients according to the Tanner-Marshall system. We accepted the onset of puberty as breast development in girls and testicular volume ≥4 cc in boys. We measured testicular volumes using a Prader orchidometer. We determined the bone ages of the patients with the left hand/wrist radiograph. The hand-wrist radiographs were evaluated by the same pediatric endocrinologist using the Greulich-Pyle radiology atlas (16).

2.2. Statistical analysis

We performed all statistical analyses on SPSS 25 software (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY, USA) and expressed descriptive statistics as frequency, rate, mean, and standard deviation for different variables. We presented percentage and % values for categorical variables and mean plus standard deviation values for continuous variables in the tables. We evaluated the research values in terms of normality of distribution and assessed them using skewness and histograms. We performed two-way comparisons between independent groups using the t-test and reported the results as mean ± standard deviation. We applied the non-parametric Mann-Whitney U test when the difference between the numbers of individuals in groups was significant and expressed the results as rank average and median values. We applied chi-square analysis to examine differences in distributions of different variables by groups and added cross tables. We regarded p levels <0.05 as significant for all results.

3. Results

Twenty-seven (61.4) of the 44 cases were girls, and 17 (38.6) were boys. Ages ranged between 0.1 and 16.6 years (11.5±3.3). Based on the Tanner-Marshall puberty staging system, 24 (54.5) patients were stage 1, nine (20.5%) were stage 2, three (13.6%) were stage 3, and five (11.4%) were stage 4. Partial GHD was present in 33 (75%) patients and complete GHD in 11 (25%). The mean height SDS before treatment was -3.3±0.8, and the mean target height SDS was -1.5±0.9. We determined maximum GH responses by the L-Dopa stimulation test in 43 cases, the clonidine stimulation test in 44, and the glucagon stimulation test in one. The mean maximum stimulated GH response was 6.1±2.8 ng/ml.

According to the results obtained, the rate of those with basal IGF-1 levels SDS <-2 is significantly lower than the rate of those with higher than basal IGF-1 levels SDS > -2 in the group with partial GH deficiency (χ^2 (1) = 12.61, p < 001) (Table-1). No significant difference was present in terms of IGFBP-3 distributions based on SDS in the cases with complete and partial GHD (p>0.05) (Table 2).

Table 1. Distribution of IGF-1 SDS by Growth Hormone Stimulation Test Results

GH Response		Deviation in IGF-1		Total
		SD <-2	SD >-2	
Partial GH Deficiency	n	1	32	33
	%	3	97	100
Komplet GH Deficiency	n	5	6	11
	%	45.5	54.5	100
Total	n	6	38	44
	%	13.6	86.4	100

IGF-1:Insulin-like growth Factor-1, GH: Growth Hormone, SDS: Standart Deviation Scores

Table 2. Distribution of IGF BP-3 SDS by Growth Hormone Stimulation Test Results

GH Response		Deviation in IGF BP-3		Total
		SD <-2	SD >-2	
Partial GH Deficiency	n	2	31	33
	%	6.1	93.9	100
Komplet GH Deficiency	n	2	9	11
	%	18.2	81.8	100
Total	n	4	40	44
	%	9.1	90.9	100

IGF BP-3:Insulin growth Factor Binding Protein-3, GH: Growth Hormone, SDS: Standart Deviation Scores

A comparison of the growth responses of patients with basal IGF-1 SDS values lower and higher than -2SD revealed that the mean rank responses of patients with severe deviations in basal IGF-1 (<-2 SDS) were significantly higher ($p<0.05$). However, there was no significant difference between the subjects with severe deviations in basal IGFBP-3 and those without in terms of growth responses ($p >0.05$) (Table 3).

Table 3. Comparison of growth response rank means according to the level of deviation in IGF-1 and IGFBP-3 values

Variables	Groups	n	Rank Average	Median	*z*	*p*
IGF -1	SD >-2	6	33.25	.94	-2.21	.025
	SD < -2	38	20.80	.37		
IGF BP-3	SD >-2	4	10.75	-.15	-1.91	.056
	SD < -2	40	23.60	.42		

IGF-1:Insulin-like growth Factor-1, IGF BP-3:Insulin growth Factor Binding Protein-3, SD: Standart Deviation

Examination of whether patients' pre-treatment height SDS, IGF-1 SDS, and IGFBP-3 SDS differed significantly from the values obtained after one year revealed that the mean values for all three parameters were significantly higher compared to the baseline ($p < 0.01$) (Table 4).

Table 4. Changes in the height SDS, IGF-1 SDS and IGF BP-3 SDS values of the cases

Variables	Period	mean	S	% 95 Confidence Interval		*t*	*p*
				Lower Limit	Upper Limit		
Height SDS	Basal	-3.39	.81	-0.77	-.32	-4.96	**.000**
	One year later	-2.83	.72				
IGF-1 SDS	Basal	-1.35	.82	-1.80	-.96	-6.56	**.000**
	One year later	.026	1.58				
IGF-BP-3 SDS	Basal	-.78	.75	-1.06	-.58	-6.81	**.000**
	One year later	.041	.93				

IGF-1:Insulin-like growth Factor-1, IGF BP-3:Insulin growth Factor Binding Protein-3, SDS: Standart Deviation Scores

Analysis of the relationship between the criteria employed in the study and growth response revealed a significant negative correlation between delta height SDS and maximum stimulated GH response, with growth response increasing as stimulated maximum GH response decreased (Table 5).

Table 5. Relationships between growth response and other metrics

Variables		Basal IG-1 SDS	Basal IGF BP-3 SDS	Peak GH Response	Target height SDS	Height SDS
Δ Height SDS	r	-.185	-.150	**-.407****	.028	-.267
	p	.230	.330	**.006**	.855	.080

*IGF-1:Insulin-like growth Factor-1, IGF BP-3:Insulin growth Factor Binding Protein-3, GH: Growth Hormone, SDS: Standart Deviation Scores **p <0 .01*

4. Discussion

GHD is one of the treatable causes of short stature in children. Due to the pulsatile nature of GH release, GH stimulation tests are required in cases of suspected GHD (17). GH secretion can be affected by factors such as age, gender, puberty, insufficient nutrition, and obesity. The pharmacological stimulus is not physiological, and the diagnostic threshold varies among different centers (18). Researchers have also emphasized the need for simpler methods for reasons such as difficulty in application, limited repeatability, side effects, cost, and the invasive nature of the procedure (19). Serum IGF-1 and IGFBP-3 levels reflect GH secretion in healthy children, and diurnal changes are very low (4). Evaluating IGF-1 and IGFBP-3 levels in children with short stature can therefore be employed as an auxiliary method for avoiding unnecessary GH stimulation tests or as a complementary tool in diagnosing GHD (20, 21). Studies have shown that IGF-1 levels lower than -2 SDS require powerful consideration of GHD (19, 22). Similarly, the present study revealed severe deviation in IGF-1 values as a significant variable in showing GHD. However, the study findings did not support those previous studies describing baseline IGFBP-3 levels as a useful diagnostic tool for showing GHD.

This study also investigated the relationship between IGF-1 and IGFBP-3 levels and growth response following GH therapy in cases of GHD. The first-year growth response after GH therapy in children with GHD is known to be one of the best indicators of long-term growth (1, 23), while GH is the primary factor determining IGF-1 levels in circulation (10). In that context, it has been assumed that the positive effects of GH therapy on growth will be parallel to the increase in IGF-1 levels (24, 25). In addition, Kim et al. (10) showed a weak correlation between IGF-1 levels and growth response in children with GHD who started GH therapy, with this relationship being observed mainly in the group with severe GHD. On the other hand, Cutfield et al. (26) determined that patients with GHD with low IGF-1 levels before GH therapy exhibited better growth responses in the first year of treatment. Kim et al. (27) showed that serum Δ IGF-I levels measured in the first year of treatment in prepubertal cases with GHD started on GH therapy and for whom GH treatment was initiated can be used as a marker to predict the growth response. However, there are also opposing views. Lanes et al. (28) found that the increase in IGF-1 SDS during GH therapy was not consistent with the increase in height and suggested that IGF-1 follow-up during treatment would be more useful in terms of safety and adherence to treatment than GH dose adjustment. In the present study, the growth responses obtained in the first year of GH therapy were significantly higher in patients with severe deviations in basal IGF-1 levels compared to the other group, the growth responses increasing in line with delta IGF-1 levels. This finding supports those studies suggesting that IGF-1 levels exhibiting severe negative deviation before GH therapy and delta IGF-1 levels evaluated in the first year of treatment may be useful in predicting the response to that treatment.

The GH-IGF-1 axis is an essential component of the endocrine system that controls linear growth in childhood

(29). IGF-1 and IGFBP-3 bind to 90% of IGF-1 in the circulation, and the acid-labile subunit are in a triple complex (30), and serum IGF-1 and IGFBP-3 levels are associated with GH levels under normal conditions (31). However, the usefulness of observing IGFBP-3 levels during GH therapy in assessing the response to treatment is controversial. IGFBP-3 has been reported to play a role in apoptosis and growth inhibition of cancer cells and be broken down by proteases after their secretion during inflammation (32,33). Functional studies have investigated the relationship between genetic polymorphism in IGFBP-3 and the response to GH therapy. Patients with GHD with the -202 A allele IGFBP3 genotype exhibited better average growth velocity and higher IGFBP-3 levels in the first year of GH therapy than patients with the -202 AC or CC IGFBP3 genotypes (34). These factors cast doubt on the use of IGFBP-3 as a diagnostic tool in evaluating the efficacy of GH therapy. Despite these disadvantages, some researchers have reported that changes in IGFBP-3 in children receiving GH therapy are significantly associated with growth response and have even suggested that IGFBP-3 may be a more useful marker than delta IGF-1 in predicting growth response (27). In the present study, we found that the increase in growth velocity in the first year in cases of GHD started on GH therapy was associated with increased IGFBP-3 levels. However, we did not observe the significant growth response seen in cases with severe deviations in basal IGF-1 levels in cases with severe deviations in basal IGFBP-3 levels.

There are several limitations to this study. The first is its single-centre nature and the low patient number. Second, we did not perform priming with sex steroids before the GH stimulation test in peripubertal children. Third, the evaluation period after GH therapy was limited to one year. And fourth, we did not apply the same GH stimulation test in all cases. We applied two separate tests, clonidine and L-Dopa, with glucagon used as the second test in only one case. Another limitation is that not all cases were in the same puberty stage.

Severe deviation in basal IGF-1 levels should strongly suggest GHD. Delta IGF-1 and delta IGFBP-3 levels evaluated in the first year of treatment, together with basal IGF-1 levels, can be a useful diagnostic tool in demonstrating growth response in children with GHD receiving GH therapy.

Conflict of interest

Authors declared that there is no conflict of interest.

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None to declare.

Authors' contributions

AA, SB: conceptualized the study; AA, SB: managed the field conduct and logistics; AA, SB: drafted the manuscript; SB: analyzed the data. All authors contributed to the critical revision of the manuscript, and its final approval.

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