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ORIGINAL ARTICLE

Determinants of early growth response to recombinant growth hormone therapy in children with isolated growth hormone deficiency

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Abstract

Growth hormone deficiency (GHD) is an important endocrine cause of short stature in childhood, occurring in approximately 1 in 4,000–10,000 live births. Early diagnosis and treatment are critical for achieving optimal height growth. This study was designed to identify factors influencing early growth response to recombinant human growth hormone (rhGH) treatment in children with isolated growth hormone deficiency (IGHD). This retrospective study included data from 205 patients diagnosed with IGHD who received rhGH treatment for at least one year at the pediatric endocrinology clinic of a tertiary children's hospital between 2009 and 2013. Isolated GHD was defined as cases meeting auxological criteria and having a peak GH response <10 ng/mL on two different GH stimulation tests. Patients were grouped into good and poor treatment response categories based on the change in height standard deviation score (Δ height SDS) during the first year of treatment. Demographic characteristics, anthropometric measurements, GH stimulation test results, serum IGF-1 and IGFBP-3 levels, pituitary magnetic resonance imaging (MRI) findings, bone age, and trace element levels were evaluated. The mean age at diagnosis was 10.5±2.9 years, and a good response to treatment was observed in three-quarters of the patients (74%). Pituitary MRI findings were not significantly

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associated with treatment response. Younger age at diagnosis, a lower peak GH response at diagnosis, and higher IGF-1 SDS after one year of treatment were associated with a better first-year growth response to rhGH therapy.

Abbreviations: GH: Growth Hormone, GHD: Growth Hormone Deficiency, IGHD: Isolated Growth Hormone Deficiency, IGF-1: Insulin-like Growth Factor-1, IGFBP-3: Insulin-like Growth Factor Binding Protein-3, rhGH: Recombinant Human Growth Hormone, MRI: Magnetic Resonance Imaging, SDS: Standard Deviation Score

Introduction

Growth serves as a fundamental indicator of pediatric health, reflecting a sophisticated interplay between genetic potential, nutritional status, and endocrine regulation. However, growth hormone (GH) is the primary determinant of linear growth, especially from the second year of life onwards. Growth hormone deficiency (GHD) is an important endocrine cause of short stature in childhood, occurring in approximately 1 in 4,000–10,000 live births [1,2]. Given its impact on final stature, early diagnosis and timely initiation of recombinant human growth hormone (rhGH) are extremely important for patients to reach their parents' target height and optimize adult height outcomes. The diagnostic workflow for GHD is multifaceted, necessitating a synthesis of clinical assessment, auxologic and biochemical evaluation. This includes the measurement of serum insulin-like growth factor-1 (IGF-1) and insulin-like growth factor binding protein-3 (IGFBP-3), provocative GH stimulation testing, and magnetic resonance imaging (MRI) of the hypothalamic–pituitary region [1,3]. Among these, auxologic parameters, specifically a significantly reduced growth velocity and a gradual decrease in height standard deviation score (SDS), are the cornerstones of clinical suspicion. The therapeutic response to rhGH is typically strongest in the first year of treatment and is characterized by a marked "catch-up" growth phase. Height gain during the first year of treatment is widely accepted as one of the most reliable indicators of long-term treatment success; an increase of approximately 0.3 to 0.5 in height SDS is generally defined as a positive response [4]. However, the degree of this response shows significant variability among individuals. While various factors influence this response, such as age at initiation of treatment, initial height SDS, rhGH dose, peak GH levels during stimulation, and average parental height, precise predictors remain a subject of ongoing clinical debate [5,6,7]. Identifying the clinical and laboratory determinants of early growth response in children with IGHD is crucial for refining therapeutic protocols and facilitating individualized patient management. Consequently, the objective of this study was to evaluate and compare the clinical, auxologic, biochemical, and radiological characteristics of "good" versus "poor" responders to determine the factors associated with optimal growth outcomes during the first year of rhGH therapy.

Materials and Methods

Ethical approval

Ethical approval for this study was obtained from the Ankara Children's Health and Diseases Hematology Oncology Training and Research Hospital Clinical Research Ethics Committee (approval number: 2015-011, approval date: April 27, 2015).

Study design and participants

This retrospective study was conducted at the pediatric endocrinology clinic of a tertiary care children’s hospital, evaluating patients followed for pathological short stature between January 2009 and December 2013. Initially, children with a height SDS below -2.0 were screened and monitored [1,8]. Inclusion criteria for further investigation were a growth velocity below the 25th percentile for age and

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sex during a minimum six-month follow-up period, following the exclusion of other etiologies for short stature. A total of 205 patients diagnosed with IGHD, based on suboptimal responses to two distinct pharmacological GH stimulation tests (L-DOPA and clonidine), were enrolled. Growth hormone deficiency was defined as a peak GH level <10 ng/mL in both tests. Patients were further stratified by deficiency severity: complete GHD (peak GH <5 ng/mL) and partial GHD (peak GH 5–10 ng/mL) [9,10]. Serum IGF-1 and IGFBP-3 levels were measured via immunochemiluminescence assay at baseline and after the first year of rhGH therapy to evaluate their association with growth response.

Clinical and auxological evaluation

Clinical and auxological data from the first year of GH therapy were obtained retrospectively from patient records. Evaluated parameters included sex, gestational age, birth weight, height, height SDS, weight, weight SDS, body mass index (BMI) and BMI SDS, target height, predicted adult height (PAH), bone age, the difference between chronological age and bone age, annual growth velocity, and the change in height SDS during the first year of treatment. Height, weight, and BMI SDS values were calculated according to the reference growth charts for Turkish children developed by Neyzi et al. [11]. First-year growth response was assessed using the change in height SDS (Δ height SDS). A good treatment response was defined as an increase of ≥0.3 SDS in children with partial GHD and ≥0.4 SDS in those with complete GHD, based on published consensus recommendations indicating that the expected first-year growth response differs according to the severity of growth hormone deficiency [12]. Target height was calculated using parental heights, and predicted adult height was predicted using the Bayley–Pinneau method [13].

Radiological evaluation

Bone age was evaluated in all patients older than one year using left wrist radiographs according to the Greulich-Pyle atlas [14]. All participants underwent magnetic resonance imaging (MRI) of the hypothalamic-pituitary region to identify structural abnormalities. Pituitary height, volume, and the presence of cystic or space-occupying lesions were among the parameters assessed. Pituitary hypoplasia was defined as pituitary height <3 mm in pre-pubescent patients and <4 mm in adolescent patients [15]. Pituitary gland measurements of the patients were standardized according to age and sex-specific percentile curves.

Treatment adherence

Treatment adherence data were available for all 205 patients. Adherence was assessed based on parent and patient reports regarding the frequency of administered injections. Skipping one or fewer doses per week was considered good adherence, whereas skipping two or more doses per week was defined as poor adherence [16].

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 22.0 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation (SD). Student's *t*-test was used to compare normally distributed variables, whereas the Mann–Whitney U test was used for variables that were not normally distributed. Categorical variables were evaluated using the chi-square test. A p-value <0.05 was considered statistically significant.

Results

Demographic and basic characteristics

A total of 205 patients diagnosed with IGHD were included in the study, with an average age of 10.5 ± 2.9 years. The sex distribution was similar; 46% were female (n=95) and 54% were male (n=110). The

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mean age at diagnosis was significantly higher in boys than in girls (p<0.05). In the first year of treatment, 74% (n=151) of patients had a good response to treatment, while 26% (n=54) had a poor response. The mean age of patients in the good response group was significantly younger than those in the poor response group (p<0.05). No significant difference was observed between sexes in terms of treatment response rates and puberty distribution (p>0.05). Similarly, gestational age and birth weight did not differ significantly according to sex or treatment response. Target height SDS differed between boys and girls (p<0.05); however, there was no significant difference in target height, target height SDS, or estimated adult height between the two response groups (Table 1).

Table 1. Demographic characteristics of the study population.

Characteristic	Total (n=205)	Distribution by sex			Distribution by treatment response		
		Girls (n=95, 46%)	Boys (n=110, 54%)	*p*	Good response (n=151, 74%)	Poor response (n=54, 26%)	*p*
Age at diagnosis (years)	10.5±2.9 (2.08–16.5)	9.8±2.7 (2.4–14.0)	10.9±3.0 (2.08–16.5)	<0.05	10.2±3.1 (2.08–16.5)	11.1±2.0 (6.07–14.1)	<0.05
Gestational age (weeks)	39.0±2.0 (24–40)	39.5±1.0 (36–40)	39.0±3.0 (24–40)	>0.05	39.7±0.9 (36–40)	38.6±3.4 (24–40)	>0.05
Birth weight (g)	3010±629 (800–4650)	3020±540 (1740–4200)	3000±714 (800–4650)	>0.05	2979±575 (900–4500)	3099±758 (800–4650)	>0.05
Target height (cm)	161.5±9.0 (139–186)	153.9±5.6 (139–166)	168.0±5.6 (151.8–186)	–	161.6±9.1 (139–186)	160.5±8.6 (143–184)	>0.05
Target height SDS	−1.4±0.9	−1.5±0.9	−1.2±0.9	<0.05	−1.4±1.0	−1.5±0.9	>0.05
Predicted adult height (cm)	156.0±8.6 (135–173.9)	148.9±5.0[a] (135–159.6)	162.1±6.0 (145–173.9)	–	156.2±8.3 (135–171)	155.7±9.1 (143–173.9)	>0.05
Prepubertal, n (%)	106 (51.7)	52 (54.7)	54 (49.1)	>0.05	80 (53.0)	26 (48.1)	>0.05
Pubertal, n (%)	99 (48.3)	43 (45.3)	56 (50.9)	>0.05	71 (47.0)	28 (51.9)	>0.05

Data are presented as mean ± SD (range) or n (%). SDS: standard deviation score. [a]Calculated from the reported total and boys' values.

Auxological and clinical outcomes

Analysis based on treatment response showed that the good responder group had a slightly lower baseline height SDS (−3.04±0.7 vs −2.93±0.6) and more pronounced bone age delay (1.75±1.1 vs 1.58±1.3 years), whereas baseline weight SDS (−1.98±1.16 vs −2.13±0.93) and pre-treatment growth velocity (4.32±0.59 vs 4.35±0.50 cm/year) were similar between the groups. After the first year of treatment, height increase (9.44±2.49 vs 6.79±1.90 cm), height SDS gain (Δ height SDS; 0.87±0.3 vs −0.01±0.3), weight SDS gain (0.32±0.84 vs −0.10±0.60), increase in growth velocity (4.64±2.24 vs 2.54±1.95 cm/year), and bone age progression (1.4±0.9 vs 1.1±0.9 years) were significantly greater in the good responder group (p<0.05).

Baseline and first-year auxological parameters according to sex are presented in Table 2. No significant difference was observed in Δ height SDS between girls and boys. The mean growth rate during the first year was 8.2 ± 2.0 cm/year for girls and 8.5 ± 2.5 cm/year for boys (p>0.05).

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Table 2. Comparison of baseline and first-year auxological parameters according to sex.

Parameter	Girls (n=95)			Boys (n=110)		
	Baseline	First year	*p*	Baseline	First year	*p*
Height (cm)	122.0±15.4	135.0±16.0	<0.001	129.0±16.0	138.0±16.0	<0.001
Height SDS	−3.0±0.6	−2.4±0.8	<0.001	−2.9±0.7	−2.3±0.8	<0.001
Weight SDS	−1.9±1.0	−1.7±1.1	0.003	−2.1±1.1	−1.9±1.2	0.022
BMI SDS	−0.50±1.0	−0.44±1.2	0.743	−0.6±1.0	−0.8±1.2	0.077
Bone age (years)	8.0±1.1	9.7±2.8	<0.001	8.9±3.2	10.3±3.1	<0.001
ΔAge–bone age (years)	1.8±1.1	1.14±0.9	<0.001	1.9±1.2	1.7±1.2	0.059
Growth velocity (cm/year)	4.3±0.5	8.2±2.0	<0.001	4.2±0.6	8.5±2.5	<0.001

Data are presented as mean ± SD. BMI: body mass index; SDS: standard deviation score; ΔAge–bone age: difference between chronological age and bone age.

Treatment adherence was high in the study cohort. Overall, 182 of 205 patients (88.8%) showed good adherence to recombinant human growth hormone therapy, while poor adherence was observed in 23 patients (11.2%) (Figure 1).

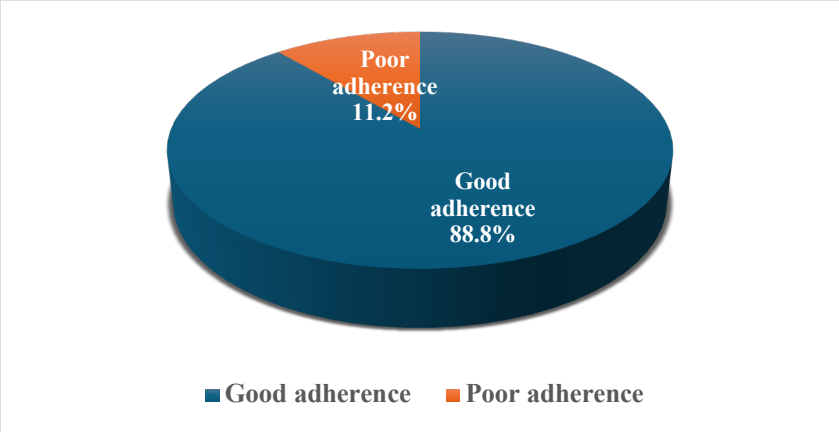


Figure 1. Treatment adherence to recombinant human growth hormone therapy among children with isolated growth hormone deficiency.

Biochemical and radiological findings

Peak GH levels in both L-DOPA and clonidine stimulation tests were significantly lower in the good-response group (L-DOPA: 2.8±2.1 vs 3.5±2.2 ng/mL, p=0.027; clonidine: 4.3±2.4 vs 5.1±1.8 ng/mL, p=0.01). The cohort consisted of 52% patients with complete GHD and 48% with partial GHD; however, the distribution of deficiency severity did not differ significantly between response groups. Serum IGF-1 and IGFBP-3 levels increased significantly in both groups during the first year of treatment. While baseline levels and one-year IGFBP-3 SDS values were similar between groups, the IGF-1 SDS at one year was significantly higher in the good response group (p=0.03) (Figure 2).

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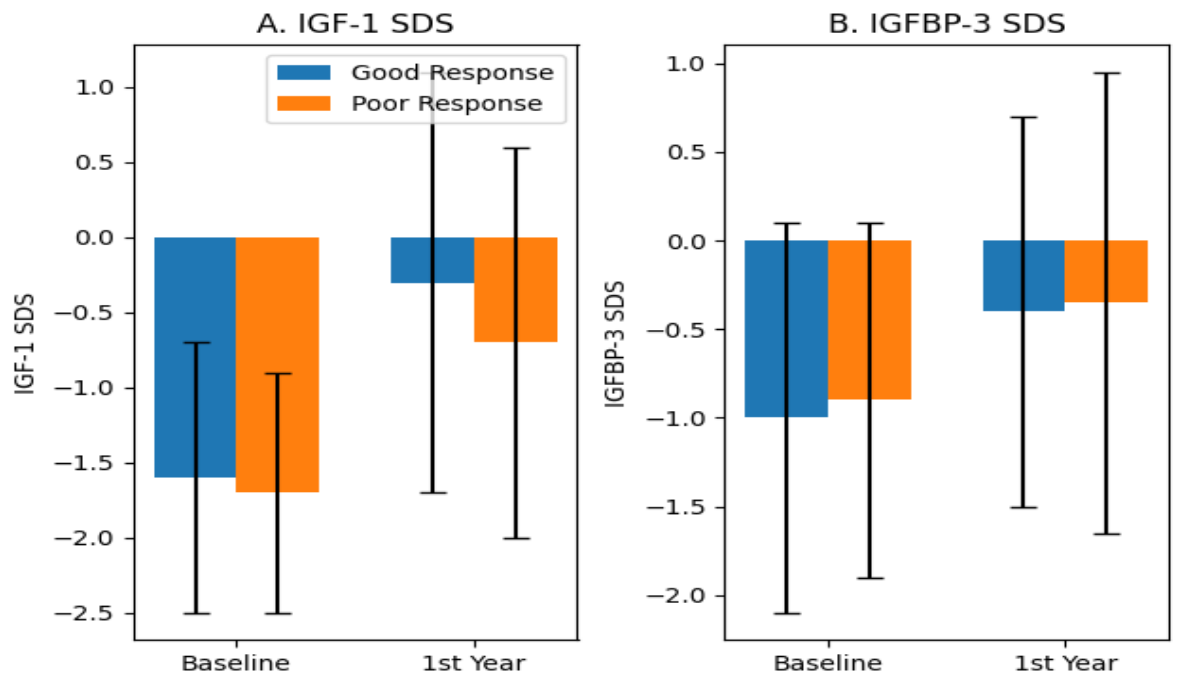


Figure 2. Changes in IGF-1 SDS and IGFBP-3 SDS at baseline and after one year of treatment according to treatment response.

Regarding radiological evaluation, 80% of the patients had normal pituitary MRI findings at diagnosis, which was more frequent in the good response group. Other findings, including pituitary hypoplasia, microadenomas, and structural abnormalities, occurred at lower frequencies; their distribution is shown in Figure 3.

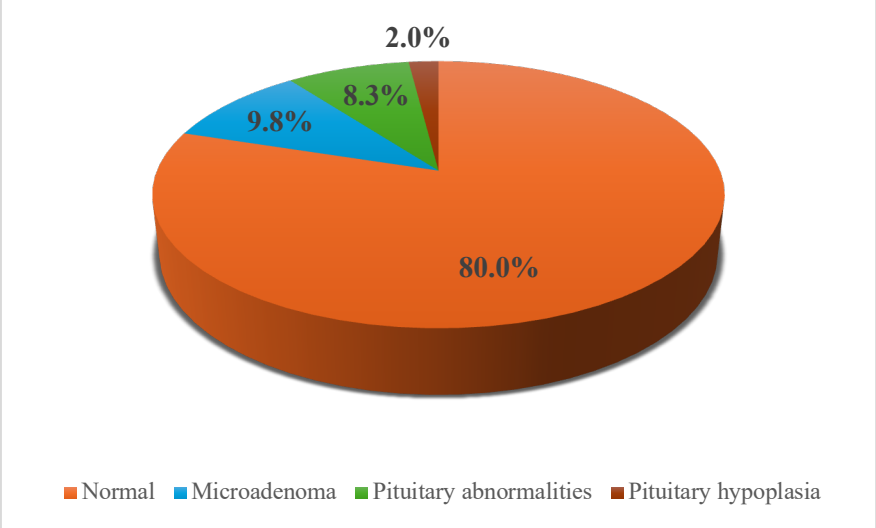


Figure 3. Distribution of pituitary abnormalities on MRI.

Craniocaudal pituitary height measurements were within normal limits in 2/3 of the patients. In addition, zinc deficiency was detected in approximately one-fifth of the cohort and iron deficiency in 14%, with zinc deficiency being significantly more common in girls than in boys (p<0.001).

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Discussion

In this study, we comprehensively evaluated the effects of auxological, biochemical, and radiological factors on recombinant human growth hormone (rhGH) treatment in children diagnosed with isolated growth hormone deficiency (IGHD) during the first year of treatment.

Age at diagnosis and pubertal status

The mean age at diagnosis in our cohort was 10.5 ± 2.9 years, which is consistent with existing literature reporting that IGHD is frequently identified during the school-age period [17,18,19,20,21]. Large-scale cohort analyses have shown that the average age at diagnosis typically ranges between 10 and 12 years [22,28]. In analyses based on the KIGS database, treatment efficacy has been evaluated primarily based on the age at treatment initiation rather than the age at diagnosis, with the median age of rhGH initiation reported at approximately 10.7 years [22]. Slightly more than half of the patients (51.7%) were in the pre-pubertal period at the start of treatment. The literature has highlighted that GH treatment initiated in the pre-pubertal period is associated with significantly greater height increase than treatment initiated in adolescence [22]. In our study, the pubertal stage was not found to be significantly related to treatment response; given the relatively even split between pre-pubertal and pubertal patients in our cohort, this factor may have had a limited overall impact on the observed growth outcomes.

Sex distribution and referral patterns

Many studies have reported a higher proportion of male patients in children evaluated for IGHD [17,18,19,20,21]. This may be attributed to referral bias rather than a biological difference, as short stature is often noticed earlier in boys by families and healthcare providers [23,24]. In a study by Henry et al. evaluating 5,880 children referred due to short stature, 63% of referrals were from boys; however, the distribution of confirmed IGHD cases was similar between sexes, and there was no significant difference between sexes in terms of disease severity, pituitary imaging findings, or the presence of isolated or multiple pituitary hormone deficiencies [25]. In our cohort, no significant difference was observed in the number of male and female patients, and female patients presented at a younger age. This likely reflects improved access to healthcare and increased awareness regarding growth monitoring in children.

GH stimulation tests and treatment response

In our study, no significant difference in treatment response was observed between patients classified as partial and complete GHD. Studies suggest that differentiating between partial and complete GHD based solely on stimulation test results has limited predictive value for treatment response. Cole et al. highlighted that GH stimulation test results alone may be insufficient to assess clinical growth response, and Darendeliler et al. noted that the methodological differences and limited reproducibility of these tests make the interpretation of cutoff values difficult [26,27]. Analyses with KIGS data have shown that growth response is influenced by numerous factors, including age at treatment initiation, baseline height SDS, and individual clinical characteristics [28,29]. These findings support our observation that treatment response is most likely determined by a multifactorial interaction of clinical and auxological variables rather than the categorical (partial vs complete) classification of GHD. Nevertheless, lower peak GH levels were associated with a better first-year response in our cohort. Similarly, Yoon et al. found no significant difference in the growth response to rhGH according to peak GH levels on stimulation testing among children with idiopathic GHD, and reported comparable growth responses in children with GHD and those with idiopathic short stature [30].

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First-year growth response and biochemical markers

The increase in height SDS during the first year of rhGH treatment was significantly greater in the good responder group than in the poor responder group. This finding confirms that substantial catch-up growth occurs during the first year of treatment. Height SDS gain during the first year is widely accepted as one of the most reliable indicators of treatment effectiveness and long-term growth outcomes in children with IGHD [12,18]. In the present study, treatment response was defined according to published consensus recommendations using different Δ height SDS thresholds for partial and complete GHD, reflecting differences in disease severity [12]. Consistent with the latest Turkish Pediatric Endocrinology Consensus Report (ÇEDD 2024) [12], our findings support the use of first-year height SDS gain as a practical and clinically meaningful indicator of early treatment response. The results of our study demonstrate that early growth response is an important indicator in determining treatment efficacy. Serum IGF-1 and IGFBP-3 are commonly used to detect the peripheral effects of GH secretion [31]. Current guidelines emphasize the individualization of GH treatment according to growth rate and serum IGF-1 levels; IGF-1 measurements taken during follow-up serve as a guide for dose adjustments [32]. In our study, while IGF-1 SDS did not differ between groups at diagnosis, it was significantly higher in the good responder group during the first year of treatment. This supports that, as highlighted in the literature, IGF-1 SDS can be used as a critical marker for monitoring the biological response to GH treatment.

Radiological findings and trace element deficiencies

In our cohort, normal pituitary MRI findings constituted the majority of imaging findings. Although normal MRI findings were numerically more common in good responders, no statistically significant association was observed between pituitary MRI findings and first-year treatment response. Previous studies have reported that structural pituitary abnormalities may be associated with more severe growth hormone deficiency and a better response to rhGH therapy [33,34]. However, our findings suggest that pituitary MRI findings alone were not a significant predictor of first-year treatment response in children with IGHD. A significant proportion of our patients had trace element deficiencies; zinc deficiency was observed in one-fifth of cases, and iron deficiency in 14%. Zinc, in particular, plays a regulatory role in the GH/IGF-1 axis, affecting linear growth, and micronutrient deficiencies may indirectly affect the growth response. Therefore, assessment and correction of trace element deficiencies may be considered as a supportive approach in the clinical management of children with IGHD [35,36].

Limitations

The main limitations of this study are its retrospective, single-center nature and the fact that the data only cover a period up to 2013. However, the large sample size and the detailed evaluation of a homogeneous IGHD patient cohort constitute the study's significant strengths.

Conclusion

In conclusion, our findings demonstrate that younger age at diagnosis, lower peak GH levels during stimulation testing, and higher IGF-1 SDS after one year of treatment were associated with a more favorable first-year growth response in children with IGHD. Although normal pituitary MRI findings were more common among good responders, pituitary MRI findings were not significantly associated with treatment response. Early diagnosis and timely initiation of rhGH therapy remain essential for optimizing growth outcomes. Future prospective multicenter studies are warranted to validate these findings.

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Conflict of interest

The authors declare that there is no conflict of interest.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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