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Growth Hormone Therapy in Neurosecretory Dysfunction

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What is already known on this topic?

- *Growth hormone neurosecretory dysfunction (GH-NSD) is one of the rare causes of short stature. It is treated with recombinant human growth hormone (rhGH). Diagnosis is challenging, and as a result, it may be overlooked and diagnosed less frequently. There is a limited number of studies published on this topic.*

What this study adds on this topic?

- *In this area, where there have been only a few studies previously, we have demonstrated that patients diagnosed with GH-NSD respond well to rhGH treatment and can achieve their genetic height potential. Additionally, we concluded that the initial height SDS, predicted adult height SDS, and mid-parental height SDS are possible factors that influence treatment response.*

ABSTRACT

Objective: Growth hormone neurosecretory dysfunction (GH-NSD) is a rare cause of short stature. Diagnosis is established by evaluating nocturnal growth hormone secretion in patients with normal growth hormone stimulation tests. The aim of this study was to evaluate the first- and second-year treatment responses and final height in patients diagnosed with GH-NSD and treated with recombinant human growth hormone (rhGH).

Materials and Methods: This retrospective study examined 500 patients treated with rhGH for short stature at a pediatric endocrinology clinic at Akdeniz University. Among them, 18 patients diagnosed with GH-NSD were included in the study. At the time of treatment initiation, parameters such as insulin-like growth factor 1 (IGF-1), growth hormone (GH) stimulation test results, mean GH level during sleep, height standard deviation score (SDS), mid-parental height (MPH), and predicted adult height (PAH) were assessed. Treatment responses during the first and second years, as well as final height data, were analyzed.

Results: GH therapy improved height velocity (HV) and overall height. The mean baseline height SDS of the patients was −3.13 ± 0.36. In the first year, Δheight SDS was 0.72 ± 0.44, and in the second year, Δheight SDS was 1.00 ± 0.70. Patients who reached their final height had a mean height SDS of −1.72 ± 0.83 and Δheight SDS of 1.46 ± 0.62. A correlation was found between the baseline height SDS, PAH SDS, MPH SDS, and first-year HV.

Conclusion: Patients with GH-NSD treated with rhGH respond well to treatment, achieving genetic height potential.

Keywords: neurosecretory dysfunction, short stature, growth hormone, GH test during sleep

INTRODUCTION

Growth is a complex process influenced by genetic, endocrine, and skeletal systems, as well as nutritional, psychosocial, and environmental factors.[1] Therefore, there are many causes of short stature. One of the most common causes of short stature seen in endocrine clinics is growth hormone deficiency (GHD). Growth hormone secretion, like many other hormones, follows a pulsatile pattern, with increased secretion, especially at night. However, there are still unknowns regarding the secretion pattern and the factors affecting the amount of secretion.[2-4] Growth hormone (GH) therapy for short stature associated with GHD has long been provided with recombinant DNA-derived human GH (rhGH).[5]

There are challenges in determining the indication for GH therapy. Various tests are employed in the diagnosis of GHD; however, some of these tests exhibit low sensitivity or are challenging to implement in practice. Furthermore, there is no consensus on the threshold value below which deficiency should be defined in the tests currently in use.[6] In general, many

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centers use a peak GH cut-off value of <10 µg/L for diagnosing GHD.[7-9] However, it has been demonstrated that low levels can also be detected in a healthy population when a cut-off threshold of 10 ng/mL is applied.[10,11]

Despite having normal peak GH levels in stimulation tests, there are patients who exhibit GHD clinical symptoms. These patients may have neurosecretory dysfunction, characterized by abnormal nighttime secretion. Some previous studies have observed a good response to rhGH therapy in cases of short stature related to GH neurosecretory dysfunction (GH-NSD).[12]

This study aimed to evaluate the treatment responses of patients with short stature who were diagnosed with GH-NSD and received rhGH therapy.

MATERIALS AND METHODS

Study Design

This was a cross-sectional, single-center, and retrospective study. This study includes data from patients under 16 years old who were followed up for short stature, diagnosed with GH-NSD, and treated with rhGH in Akdeniz University Pediatric Endocrinology Clinic between 1997 and 2023. Data from a total of 500 patients who received rhGH were reviewed from the hospital's digital database and the national medication reporting system. From this group, patients diagnosed with GHD based on clonidine stimulation test and levodopa (L-DOPA) stimulation tests, patients diagnosed as small for gestational age (SGA), patients receiving rhGH therapy for any syndrome, patients with growth hormone resistance, those with multiple pituitary hormone deficiencies, patients with GHD secondary to radiotherapy/surgery, patients receiving additional GnRH analog therapy, and patients diagnosed with Turner syndrome and any other syndromes as well as chronic illnesses were excluded from the study.

GH secretion was evaluated using 2 standard stimulation tests (L-DOPA and clonidine). For the diagnosis of reduced GH secretion, a peak GH cut-off level of 10.0 µg/L was used.[7,8] GH deficiency was ruled out if peak GH was >10.0 µg/L in either or both tests. For patients suspected of GH-NSD, a sleep GH test was performed. An indwelling catheter was inserted in all patients before they went to sleep. After 1 hour of sleep, 8 blood samples were taken at 30-minute intervals. Patients with a mean GH level of <3 µg/L were diagnosed with GH-NSD. GH-NSD was defined when the overnight profile showed <3 spontaneous peaks of GH ≥6.7 µg/L.[13,14] A total of 18 patients who met these criteria were included in the study.

Diagnosis and Treatment Procedure of GH-NSD

GH-NSD was diagnosed based on the following criteria.[13,14]

1. Height < −2 standard deviation score (SDS) for age
2. Insufficient growth velocity (HV)
3. GH level > 10 µg/L in one or both provocative GH tests.
4. Delayed bone age (2 years)
5. Mean GH level during sleep < 3 µg/L.
6. GH-NSD was defined when the overnight profile showed <3 spontaneous peaks of GH ≥6.7 µg/L.
7. No accompanying chronic diseases or genetic disorders.

Patients diagnosed with GH-NSD were started on an initial dose of 0.033 mg/kg/day of rhGH. Throughout the follow-up period, the drug dose was modified according to the patient's HV and insulin-like growth factor 1(IGF-1) SDS values.

Clinical and Laboratory Investigations

In all patients, IGF-I serum concentration was evaluated in blood samples obtained in the morning prior to the first GH stimulation test. The results were presented as IGF-I SDS according to age and sex.[15]

The procedure of the clonidine stimulation test was as follows: Before the test began, 5 mg/kg of clonidine was given orally to the patients. Blood specimens were collected at 0, 30, 60, and 90 minutes to measure GH. In the L-DOPA stimulation test, 10

Table 1. General Clinical Features of the Patients

	All Patients
Sex (M/F)	8/10
At the start of treatment	
CA	10.14 ± 3.25
Weight SDS	−2.99 (−3.28/−1.72)
Height SDS	−3.13 ± 0.36
BMI SDS	−1.20 ± 1.15
BA	8.09 ± 3.04
PAH Male Female	 164.01. ±7.49 150.30 ± 4.89
PAH SDS	−1.97 ± 0.71
MPH Male Female	 165.85 ± 3.92 155.21 ± 4.77
MPH SDS	−1.47 ± 0.59
IGF1 SDS	−1.36 ± 0.42
Peak GH on provocative test	14.40 ± 10.37
Mean GH during sleep	2.80 (1.95/2.90)
At the end of the first year of the treatment	
Height SDS	−2.42 ± 0.63
IGF1 SDS	−0.25 ± 0.42
HV (cm)	9.19 ± 3.11
HV SDS	1.48 ± 0.55
HV SDS <0.5 SDS/>0.5 SDS <0.3 SDS/>0.3 SDS	 9/9 5/13
Δheight SDS	0.72 ± 0.44
At the end of the second year of the treatment	
Height SDS	−2.15 ± 0.76
IGF1 SDS	0.43 ± 0.77
HV (cm)	6.30 ± 0.77
HV SDS	0.70 ± 0.65
Δheight SDS (first to second year)	0.27 ± 0.34
Δheight SDS (treatment initiation to second year)	1.00 ± 0.70

Data are expressed as mean ± SD or median (25th-75th percentile) or as frequency (percentages). BA, the bone age; BMI, body mass index; CA, chronological age; F, female; GH, growth hormone; HV, height velocity; IGF1, insulin-like growth factor 1; M, male; MPH, midparenteral height; PAH, predictive adult height; SDS, standard deviation score.

mg/kg of L-DOPA was given orally. Blood specimens were collected at 0, 30, 60, and 90 minutes to measure GH.

The height, weight, and body mass index (BMI) values of the patients at the start of treatment, first year, second year, and after the treatment were recorded. Height, weight, and BMI SDS values were calculated based on the reference values for Turkish children.[16] BMI was calculated as follows: weight was divided by the square of height (kg/m^2). Pubertal stage was assessed using the Marshall and Tanner criteria.[17] Bone age was assessed based on the Greulich and Pyle method.[18] The predicted adult height (PAH) was estimated by the Bayley-Pinneau method for patients.[19] For patients with BA < 6 years, PAH was estimated by the Roche-Wainer-Thissen method.[20] Mid-Parental Height (MPH) was calculated using the following formulas: for females (mother's height+father's height – 13) / 2, and for males (mother's height+father's height+13) / 2. Final height was considered to be achieved when bone age reached 15 years for females and 16 years for males.

Ethics

Our cases were examined considering the Declaration of Helsinki. The study was authorized by the ethics committee of Akdeniz University (Approval date: October 31, 2024, Approval No: TBAEK-713). Informed consent was obtained.

Statistical Analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences version 23.0 (IBM SPSS Corp.; Armonk, NY, USA). Categorical measurements were presented as frequency and percentages. The distribution pattern of the data was evaluated using the Kolmogorov-Smirnov (K-S) test. Normally distributed data were presented as mean ± SD, and non-normally distributed data were presented as median (25th-75th percentile). Normally distributed variables were evaluated using the Student's t-test, and non-normally distributed variables were evaluated using the Mann-Whitney U test. A *P*-value of <.05 was considered significant. A correlation analysis was performed using the Pearson test on normally distributed continuous numerical data. The strength of the relationship was interpreted based on the following *r* values: very weak (< 0.25), weak (0.26 to 0.49), medium (0.50 to 0.69), high (0.70 to 0.89), and very high (0.90 to 1.0). A *P*-value of < .05 was considered statistically significant.

RESULTS

Clinical Features of the Patients at the Start of Treatment, in the First Year and in the Second Year

A total of 18 patients with short stature and diagnosed with GH-NSD were included in the study. All patients completed the second year of their treatment. Eight of the patients were male (44.4%) and 10 were female (55.6%). At the start of treatment, the mean age of the patients was 10.14 ± 3.25 years, and the mean bone age was 8.09 ± 3.04 years. The mean height SDS was –3.13 ± 0.36, the mean PAH SDS was –1.97 ± 0.71, and the mean MPH SDS was –1.47 ± 0.59 (Table 1).

Despite the patients having high peak GH levels on provocative tests, the mean GH during sleep was 2.80 (1.95/2.90). In the assessment conducted in the first year of treatment, the mean height SDS was –2.42 ± 0.63, and the mean HV SDS was 1.48 ± 0.55. During the first year of treatment, the Δheight SDS was 0.72 ± 0.44. In 50% (9/18) of the patients, the HV SDS in the first year was >0.5 SDS. The median HV before treatment was 3.73 (3.00/4.00), whereas in the first year, the mean HV was 9.19 ± 3.11, and in the second year, it was 6.30 ± 0.77.

The mean Δheight SDS between the first and second years of treatment was 0.27 ± 0.34. After a total of 2 years of treatment,

Table 2. Features of Patients Whose Treatment Was Completed

	Patients reached final height (n = 9)
Sex (M/F)	5/4
At the start of treatment	
CA	12.02 ± 1.79
Weight SDS	–3.22 (–3.40/–1.99)
Height SDS	–3.16 ± 0.35
BMI SDS	–1.56 ± 1.27
BA	9.65 ± 2.07
PAH	
Male	164.15 ± 10.21
Female	151.18 ± 4.54
PAH SDS	–1.62 ± 0.52
MPH	
Male	163.52 ± 3.75
Female	154.20 ± 4.93
MPH SDS	–1.34 ± 0.71
IGF1 SDS	–1.28 ± 0.47
Peak GH on provocative test	12.92 ± 9.88
Mean GH during sleep	2.80 (2.00/2.85)
At the end of the first year of the treatment	
Height SDS	–2.44 ± 0.83
IGF1 SDS	–0.48 ± 0.30
HV (cm)	9.71 ± 3.99
HV SDS	1.44 ± 1.43
HV SDS	
<0.5 SDS/>0.5 SDS	5/4
<0.3 SDS/>0.3 SDS	4/5
Δheight SDS	0.74 ± 0.53
At the end of the second year of the tratment	
Height SDS	–2.04 ± 0.97
IGF1 SDS	0.28 ± 0.82
HV (cm)	6.45 ± 0.80
HV SDS	1.01 ± 0.34
Δheight SDS (first to second year)	0.40 ± 0.30
Δheight SDS (treatment initiation to second year)	1.14 ± 0.74
Final height	
Male	164.70 ± 3.93
Female	150.82 ± 4.72
Final height SDS	–1.72 ± 0.83
Δheight SDS (treatment initiation – end of the treatment)	1.46 ± 0.62

Data are expressed as mean ± SD or median (25th - 75th percentile) or as frequency (percentages). BA, the bone age; BMI:, body mass index; CA, chronological age; F, female; HV, height velocity; IGF1, insulin-like growth factor 1; M, male; PAH, predictive adult height; MPH, midparenteral height; SDS, standard deviation score.

Table 3. Comparison of Features of Male and Female Patients

	Female (n = 10) (55.6%)	Male (n = 8) (44.4%)	*P*
At the start of treatment			
CA	9.81 ± 2.11	11.47 ± 3.52	.23[a]
Weight SDS	−2.84 (−3.35/−1.47)	−2.70 (−3.30/−1.62)	.96[b]
Height SDS	−3.04 ± 0.63	−3.20 ± 0.26	.51[a]
BMI SDS	−1.26 ± 1.23	−0.95 ± 1.24	.60[a]
BA	7.80 ± 2.10	9.18 ± 3.11	.27[a]
PAH	150.30 ± 4.89	164.01 ± 7.49	<.001[a]
PAH SDS	−2.17 ± 0.80	−1.96 ± 1.19	.66[a]
MPH	155.21 ± 4.77	165.85 ± 3.92	<.001[a]
MPH SDS	−1.31 ± 0.82	−1.61 ± 0.64	.40[a]
IGF1 SDS	−0.77 ± 0.68	−0.86 ± 1.06	.83[a]
Peak GH on provocative test	14.23 ± 8.01	11.11 ± 7.48	.41[a]
Mean GH during sleep	2.80 (2.30/2.90)	2.35 (1.90/2.90)	.71[b]
At the end of the first year of the treatment			
Height SDS	−2.54 ± 0.86	−2.63 ± 0.64	.79[a]
IGF1 SDS	−0.03 ± 0.56	−0.10 ± 0.61	.82[a]
HV (cm)	7.85 ± 1.60	9.38 ± 3.23	.20[a]
HV SDS	1.22 ± 1.06	1.41 ± 0.87	.67[a]
Δheight SDS	0.51 ± 0.40	0.61 ± 0.45	.61[a]
At the end of the second year of the teratment			
Height SDS	-2.20 ± 0.86	-2.35 ± 0.92	.72[a]
IGF1 SDS	0.02 ± 0.67	0.54 ± 0.94	.19[a]
HV (cm)	6.74 ± 1.08	6.56 ± 1.22	.74[a]
HV SDS	0.84 ± 0.98	0.62 ± 0.91	.63[a]
Δheight SDS (frst to second year)	0.34 ± 0.37	0.28 ± 0.37	.77[a]
Δheight SDS (treatment initiation to second year)	0.85 ± 0.61	0.90 ± 0.75	.87[a]

[a]Student's *t*-test.
[b]Mann–Whitney *U* test
Data are expressed as mean ± SD or median (25th–75th percentile) or as frecuency (percentages). BA, the bone age; BMI, body mass index; CA, chronological age; F, female; GH, growth hormone; HV, height velocity; IGF1, insulin-like growth factor 1; M, male; MPH, midparenteral height; PAH, predictive adult height; SDS, standard deviation score.

the mean Δheight SDS was 1.00 ± 0.70. As a result, the patients' mean height SDS was −2.15 ± 0.76 in the second year.

Clinical Features of Patients Who Have Completed Treatment

Some of the patients completed their treatment and reached their final height (n: 9). The mean age at the start of treatment for these patients was 12.02 ± 1.79 years. The mean height SDS at the start of treatment was −3.16 ± 0.35. The Δheight SDS at the first year was 0.74 ± 0.53, and the Δheight SDS at the second year was 1.14 ± 0.74. At the end of the treatment, the mean final height of the patients was 164.70 ± 3.93 cm for males and 150.82 ± 4.72 cm for females. The mean final height SDS was -1.72 ± 0.83, and the mean Δheight SDS was 1.46 ± 0.62 (Table 2).

Clinical Characteristics of Patients Based on Sex and Pubertal Status

When the patients were analyzed separately by sex, the mean age of females was 9.81 ± 2.11 years, and the mean age of males was 11.47 ± 3.52 years. The mean height SDS for females was −3.04 ± 0.63, and for males, it was −3.20 ± 0.26 (P = 0.51). In the evaluations conducted during the first and second years of treatment, no significant differences were found between females and males in parameters such as height SDS, HV SDS, and Δheight SDS (Table 3).

The patients were divided into 2 groups, prepubertal and pubertal, based on their clinical findings at the start of treatment (Table 4). Eight patients (44.4%) were prepubertal, and 10 (55.6%) were pubertal. The mean age of the prepubertal patients was 8.62 ± 2.72 years, while the mean age of the pubertal patients was 12.10 ± 1.94 years (P = .006). The mean height SDS of the prepubertal group was −3.25 ± 0.57, and the mean height SDS of the pubertal group was −3.00 ± 0.42 (P = .30). In the second year of treatment, although the Δheight SDS was higher in the pubertal group, no statistically significant difference was found (prepubertal group mean Δheight SDS 0.75 ± 0.56, pubertal group mean Δheight SDS 0.97 ± 0.74) (P = .49) (Table 4).

Factors Affecting Treatment Outcomes

We examined the correlation between some parameters at the start of treatment, such as height SDS, BMI SDS, bone age, PAH SDS, MPH SDS, IGF-1 SDS, peak GH on the provocative test, and mean GH during sleep, with parameters that could be used to assess treatment outcomes. A correlation was found between height SDS and height SDS at the first year and height SDS at the second year (r = 0.83/r = 0.61, P < .001/P = .006, respectively). A correlation was found between bone age and HV at the first year (r = 0.48, P = .05). A correlation was found

Table 4. Comparison of Features of Prepubertal and Pubertal Patients

	Prepubertal (n = 8) (44.4%)	Pubertal (n = 10) (55.6%)	*P*
At the start of treatment			
CA	8.62 ± 2.72	12.10 ± 1.94	.006[a]
Weight SDS	−2.80 (−2.99/−1.55)	−2.86 (−3.42/−1.55)	.79[b]
Height SDS	−3.25 ± 0.57	−3.00 ± 0.42	.30[a]
BMI SDS	−0.90 ± 1.15	−1.30 ± 1.28	.49[a]
BA	6.43 ± 2.40	10.00 ± 1.47	.01[a]
PAH SDS	−2.33 ± 0.62	−1.87 ± 1.17	.32[a]
MPH SDS	−1.68 ± 0.75	−1.25 ± 0.71	.22[a]
IGF1 SDS	−0.76 ± 0.84	−0.85 ± 0.89	.84[a]
Peak GH on provocative test	12.27 ± 8.84	13.30 ± 7.15	.78[a]
Mean GH during sleep	2.85 (2.20/2.90)	2.60 (1.85/2.85)	.17[b]
At the end of the first year of the treatment			
Height SDS	−2.81 ± 0.85	−2.40 ± 0.65	.26[a]
IGF1 SDS	0.04 ± 0.53	−0.15 ± 0.61	.49[a]
HV (cm)	7.38 ± 1.42	9.46 ± 2.85	.08[a]
HV SDS	1.10 ± 1.20	1.146 ± 0.74	.44[a]
Δheight SDS	0.43 ± 0.41	0.65 ± 0.41	.29[a]
At the end of the second year of the treatment			
Height SDS	−2.50 ± 0.88	−2.08 ± 0.85	.32[a]
IGF1 SDS	0.24 ± 0.84	0.26 ± 0.85	.96[a]
HV (cm)	6.82 ± 1.17	6.53 ± 1.11	.59[a]
HV SDS	0.86 ± 1.08	0.65 ± 0.84	.65[a]
Δheight SDS (first to second year)	0.31 ± 0.31	0.32 ± 0.41	.96[a]
Δheight SDS (treatment initiation to second year)	0.75 ± 0.56	0.97 ± 0.74	.49[a]

[a]Student's *t*-test.
[b]Mann–Whitney *U* test.
Data are expressed as mean ± SD or median (25th-75th percentile) or as frequency (percentages). BA, the bone age; BMI, body mass index; CA, chronological age; F, female; GH, growth hormone; HV, height velocity; IGF1, insulin-like growth factor 1; M, male; MPH, midparenteral height; PAH, predictive adult height; SDS, standard deviation score.

between PAH SDS and height SDS at the first year, height SDS at the second year, HV at the first year, HV SDS at the first year, HV at the second year, and Δheight SDS at the first and second years. A correlation was found between MPH SDS and height SDS at the first and second years, HV SDS at the first year, and Δheight SDS at the first year. Additionally, a negative correlation was found between IGF-1 SDS and HV (Table 5).

DISCUSSION

This study evaluates the treatment outcomes of 18 patients diagnosed with GH-NSD and receiving rhGH therapy. Of the patients, 44.4% were male, and 55.6% were female. Unlike patients receiving treatment for GHD, the proportion of males was not significantly higher.[21-23] In previous studies focusing on patients treated for GH-NSD, a female predominance of 78.7% was reported.[12] Among the patients, 44% were prepubertal.

Patients who initiated GH therapy at an earlier age demonstrated a more favorable response to treatment.[24] In our study, the mean age of patients was 10.14 ± 3.25 years. Similarly, previous research on GH-NSD patients reported a comparable mean age of 10.17 ± 2.13 years.[12] That same study suggested that while the treatment initiation age for GH-NSD patients appeared later compared to GHD cases, GH-NSD typically manifests around puberty. From a different perspective, it is possible that these patients experienced a delayed diagnosis. A review of patients diagnosed with idiopathic short stature (ISS) also reported a treatment initiation age of 10.42 years.[25] In our cohort, 44% of patients were prepubertal; however, previous studies have indicated a lower percentage of pubertal patients in contrast.[12,24]

In our study, the mean height SDS of patients at the start of treatment was −3.13 ± 0.36, significantly below their mean parental height SDS (−1.47 ± 0.59). In a cohort evaluating a large number of GHD cases, height SDS was found to be −2.7 ± 0.8.[26] Similarly, reviews on patients with ISS reported comparable values.[25,27] Naturally, these values can fluctuate due to various factors, including the age at diagnosis and ethnic background. Prior to treatment, the median HV of patients was 3 (3/4) cm/year, which increased in the first year to a mean HV of 9.19 ± 3.11 cm/year and a mean HV SDS of 1.48 ± 0.55. By the first year, mean height SDS improved to −2.42 ± 0.63. In a study on GH-NSD patients, the first year mean height SDS was reported as −2.07 ± 0.48.[12] Spiliotis et al,[28] in their analysis of GHD and GH-NSD patients, found similar outcomes. They also reported that 80.3% of patients had an increase in height SDS >0.3, and 78.7% had an increase >0.5 SDS. In our cohort, the first year mean Δheight SDS was 0.72 ± 0.44, with 72.2% of patients showing an increase >0.3 SDS and 50% showing an increase >0.5 SDS. In summary, the mean HV values and

Table 5. Correlation of some features and parameters indicating treatment response

	Height SDS (1 year)	HV (cm) (1 year)	HV SDS (1 year)	Δheight SDS (1 year)	Height SDS (2 years)	HV (cm) (2 years)	HV SDS (2 years)	Δheight SDS (2 years)
Height SDS	$r = 0.83^{**}$ $P < .001$	$r = 0.17$ $P = .47$	$r = 0.38$ $P = .11$	$r = 0.28$ $P = .24$	$r = 0.61^{**}$ $P = .006$	$r = -0.05$ $P = .83$	$r = 0.19$ $P = 0.43$	$r = 0.04$ $P = .86$
BMI SDS	$r = 0.29$ $P = .24$	$r = -0.05$ $P = .81$	$r = 0.21$ $P = .39$	$r = 0.05$ $P = .84$	$r = 0.02$ $P = .91$	$r = -0.43$ $P = .07$	$r = -0.15$ $P = .53$	$r = -0.26$ $P = .28$
BA	$r = 0.02$ $P = .92$	$r = 0.48^{*}$ $P = .04$	$r = 0.06$ $P = .79$	$r = 0.04$ $P = .85$	$r = 0.10$ $P = .67$	$r = 0.07$ p.0.76	$r = 0.01$ $P = .95$	$r = 0.14$ $P = .57$
PAH SDS	$r = 0.59^{**}$ $P = .09$	$r = 0.67^{**}$ $P = .02$	$r = 0.57^{*}$ $P = .01$	$r = 0.70^{**}$ $P = .01$	$r = 0.74^{**}$ $P < .001$	$r = 0.37$ $P = .13$	$r = 0.62^{**}$ $P < .001$	$r = 0.74^{**}$ $P < .001$
MPH SDS	$r = 0.74^{**}$ $P < .001$	$r = 0.28$ $P = .24$	$r = 0.49^{*}$ $P = .03$	$r = 0.48^{*}$ $P = .04$	$r = 0.76^{**}$ $P < .001$	$r = 0.16$ $P = .52$	$r = 0.43$ $P = .07$	$r = 0.46$ $P = .05$
IGF1 SDS	$r = -0.23$ $P = .34$	$r = -0.47^{*}$ $P = .04$	$r = -0.25$ $P = .30$	$r = -0.45$ $P = .05$	$r = -0.32$ $P = .18$	$r = -0.18$ $P = .46$	$r = -0.21$ $P = .39$	$r = -0.44$ $P = .06$
Peak GH on provocative test	$r = 0.00$ $P = .98$	$r = 0.02$ $P = .92$	$r = 0.20$ $P = .40$	$r = 0.23$ $P = .35$	$r = 0.12$ $P = .62$	$r = 0.11$ $P = .64$	$r = 0.13$ $P = .58$	$r = 0.30$ $P = .22$
Mean GH during sleep	$r = -0.46$ $P = .05$	$r = -0.23$ $P = .34$	$r = -0.44$ $P = .06$	$r = -0.15$ $P = .53$	$r = -0.29$ $P = .23$	$r = 0.08$ $P = .74$	$r = -0.22$ $P = .36$	$r = 0.04$ $P = .85$

Pearson test.
$^{*}P < .05$; $^{**}P < .01$.
BA, the bone age; BMI, body mass index; GH, growth hormone; HV, height velocity; IGF1, insulin-like growth factor 1; MPH, midparenteral height; PAH, predictive adult height; SDS, standard deviation score.

mean height SDS of our patients increased after treatment, consistent with previous reports on patients with GHD and GH-NSD diagnoses.

In the second year of treatment, the mean height SDS of patients was −2.15 ± 0.76, with an HV SDS of 0.70 ± 0.65. Δheight SDS between the first and second years was 0.27 ± 0.34, and Δheight SDS from the start of treatment to the second year was 1.00 ± 0.70. Similar to previous studies, the highest HV was observed in the first year of treatment.[29,30]

Among all the patients, 9 had reached their final height. The mean height of females was 150.82 ± 4.72 cm, and the mean height of males was 164.70 ± 3.93 cm. At the start of treatment, the height SDS of these patients was −3.16 ± 0.35, and their final height SDS was −1.72 ± 0.83. The Δheight SDS from the beginning to the end of treatment was 1.46 ± 0.62. They had nearly reached their genetic potential (MPH SDS −1.34 ± 0.71). In a recent review evaluating 2206 patients diagnosed with idiopathic short stature (ISS), the Δheight SDS (standard deviation score for height) was found to be 1.06 ± 0.30 among the patients.[31]

When we grouped the patients by sex and compared their data, no significant differences were found between the groups. Similarly, when we divided the patients into prepubertal and pubertal groups and compared them, no significant differences were observed. We examined the correlation between several parameters, such as the patient's height SDS, BMI SDS, bone age, PAH SDS, MPH SDS, IGF-1 SDS, peak GH on the provocative test, and mean GH during sleep, with parameters that could be used to assess treatment outcomes. We found correlations between the initial height SDS, PAH SDS, MPH SDS, and some of the parameters used to evaluate the treatment response. Based on these data, we can infer that if the height SDS or genetic potential is better at the start of treatment, the treatment response will also be better. Cole et al and Reiter et al[32,33] have also shown that MPH is associated with treatment response in the first year.

If we were to discuss the limitations of the study, the sample size is small. The reason for this is that the diagnosis of NSD is complex, and it is caused by a rare form of short stature. Additionally, not all of the patients have attained their final height. Therefore, studies with greater sample sizes are needed. Another issue is the lack of a definitive consensus on the diagnosis of neurosecretory dysfunction and the fact that diagnostic criteria have been defined in only a limited number of studies. When planning our study, we took into account the criteria used in previous centers and specified the criteria we applied in the materials and methods section. Despite all these limitations, we hope that our study will provide valuable insights to other researchers in this field.

In conclusion, the mean height SDS values of patients diagnosed with GH-NSD increased with rhGH treatment, and they approached their genetic height potential. MPH SDS is one of the possible factors influencing treatment response. GH-NSD should be considered in patients with normal GH stimulation tests but presenting with short stature.

Data Availability Statement: The data that support the findings of this study are available on request from the corresponding author.

Ethics Committee Approval: This study was approved by the Ethics Committee of Akdeniz University (approval No: TBAEK-713; date: October 31, 2024).

Informed Consent: Written informed consent was obtained from the patients' parents who agreed to take part in the study.

Peer-review: Externally peer-reviewed.

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K.Ç., Y.F.B.; Analysis and/or Interpretation – E.B.Ç., M.P.; Literature Search – E.B.Ç., M.P.; Writing – E.B.Ç., M.P.; Critical Review – E.B.Ç., H.T., M.P.Declaration of Interests: The authors have no conflict of interest to declare.

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