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Evaluation of Growth Characteristics and Final Height of Cases Diagnosed with Noonan Syndrome on Growth Hormone Treatment

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What is already known on this topic?

Short stature is a common characteristic of Noonan syndrome (NS), with many individuals' adult height remaining below the third percentile. Growth hormone (GH) treatment has been shown to be beneficial in improving height outcomes in patients with NS.

What this study adds?

This study presents national data on the efficacy and safety of GH in children and adolescents with NS. The findings confirm that GH treatment significantly increased final height in children and adolescents with NS, with a mean increase of approximately + 1.4 standard deviation scores. GH treatment was demonstrated to be safe for patients with NS, with no significant side effects observed and stable cardiac findings in those with hypertrophic cardiomyopathy.

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Abstract

Objective: Proportional short stature is one of the most important features of Noonan syndrome (NS), and adult height often remains below the third percentile. Although the pathophysiology of short stature in NS patients is not fully understood, it has been shown that growth hormone (GH) treatment is beneficial in NS, significantly improving height in respect to the results of short and long-term GH treatment.

Methods: In this national retrospective cohort study, patients with NS who reached final height from 14 centers were evaluated. Patients were stratified by sex and treatment with or without GH and final height outcomes were compared.

Results: The study included 67 patients with NS, of whom 53 (79.1%) with mean follow-up 5.6 years, received GH treatment. At presentation height standard deviation scores (SDS) of the subjects who were started on GH tended to be shorter than those who did not (-3.26 ± 1.07 vs. -2.53 ± 1.23). In girls mean final height and final height SDS in those using GH vs not using GH were 150.1 cm (-2.17 SDS) vs. 147.4 cm (-2.8 SDS), respectively, and for boys these values were 162.48 cm (-1.81 SDS) vs 157.46 cm (-2.68 SDS), respectively. The Δheight SDS value of the cases was significantly higher in the group receiving GH compared to those not receiving GH (1.36 ± 1.12 SD vs. -0.2 ± 1.24, $p < 0.001$). Cardiac findings remained stable in two patients with hypertrophic cardiomyopathy who received GH treatment. No significant side effects were observed in any patient during follow-up.

Conclusion: In patients with NS who reach their final height, a significant increase in height was observed with GH treatment. An increase of approximately + 1.4 SDS may be achieved. GH treatment appears to be safe and effective in NS.

Keywords: Final height, growth hormone, Noonan syndrome, treatment

Introduction

Noonan syndrome (NS; OMIM 163950) is an inherited, multisystemic disease that occurs in 1/1000-1/2500 live births and is characterized by unique phenotypic findings (1). Mutations in the RAS-mitogen-activated protein kinase (RAS-MAPK) pathway cause NS by altering protein-coding genes. In most cases, the genetic mutations that cause NS are "gain-of-function" mutations and lead to RAS/MAPK hyperactivation, which causes the NS phenotype (2).

One of the main features of NS is postnatal-onset, proportionate, short stature and is the most common reason for presentation to pediatric endocrinology clinics (1,3). Growth rate decreases in the first year of life after birth and in the first year height standard deviation (SD) scores (SDS) loss of 1.5 SD and weight increase loss by 2 SD have been reported (4,5). Compared to the general population, in adults with NS final height is generally short. In addition, a prolonged growth period due to pubertal delay and retardation in bone age are among the growth characteristics (6).

Although the pathophysiology of short stature in patients with NS is not fully understood, the cause of short stature is multifactorial, and response to growth hormone (GH) stimulation tests may be variable. In terms of endogenous GH, there may be a deficiency, neurosecretory dysfunction, or mild GH resistance although insulin-like growth factor-1 levels are at low normal ranges (7,8,9). GH treatment has been shown to be benefiical in NS, and significantly improves height in studies with both short and long-term GH administration (7,9-24). However, questions remain unanswered about some aspects of growth in NS, including the effectiveness and safety of GH treatment in NS. Furthermore, predictive models are not yet practical as they are not sufficiently reliable for predicitng "target heights" in families with a child affected by NS. This is becuase potential genetic growth in NS are not yet fully understood given the generaly different pattern of growth, which limits the utility of current models. In particular, final height studies are lacking, with inconsistent findings and variable age at last follow-up. There is no data on the final heights of NS cases with or without GH treatment in the Turkish population.

The aim of this study was to evaluate the efficacy of GH therapy in children and adolescents with NS in the Turkish population and who had attained final height. Retrospective analysis of presenting characteristics and final heights of patients, with and without GH treatment, was performed to identify factors affecting final height in this population.

Methods

Patient Selection

The study was conducted with multiple centers across Türkiye with clinical links to the Turkish Pediatric Endocrinology and Diabetes Association. Patients followed up with a diagnosis of NS based on genetic analysis and/or Van der Burgt (25) criteria and who had reached their final height were included. The study was cross-sectional and was conducted between September 2022 and January 2024. The study was designed by the Turkish Pediatric Endocrinology and Diabetes Association "Noonan Syndrome Working Group", and centers with Pediatric Endocrinology specialists were invited to participate. Centers caring for patients with NS and who had reached their final height were selected, and

demographic and clinical information was collected through the data collection form.

Patient information was obtained from patients' medical records. Anthropometry and physical examination findings at diagnosis and at follow-up, laboratory evaluations, the result of systemic disease screening, and responses to GH treatment were evaluated. At presentation and final follow-up, age, puberty stage (Tanner staging), height and height SDS, Ranke height SDS, body mass index (BMI), BMI SDS, and bone age were evaluated. Target height (cm), target height SDS, the difference between target height SDS and presentation height SDS, age at completion of puberty, final height (cm), final height SDS, the difference between target height SDS and final height SDS, and final bone age were recorded. For patients receiving GH treatment, additional variables included age at initiation of GH treatment, duration of GH treatment, timing of GH treatment dose increases, age, height (cm), and height SDS at cessation of GH treatment, and GH dose (mcg/kg/day) were recorded. ΔHeight SDS was defined as the difference between the height SDS at the first year of follow-up in those who did not receive GH and the height SDS at the time of admission, the difference between the beginning of GH treatment and after the first year of treatment in those who received GH.

Weight and height SD values were calculated according to Turkish children norms created by Neyzi et al. (26) and standard curves for NS created by Ranke et al. (27). Growth velocity was calculated, and puberty staging was assessed according to Tanner staging. Left wrist radiographs were evaluated using the Greulich-Pyle Atlas for bone age assessment.

Criteria for inclusion in the study were:

1) Age at diagnosis is < 18 years;

2) Confirmed diagnosed of NS by Van der Burgt (25) clinical criteria and/or genetic analysis;

3) Having achieved near final height (bone age reaching ≥14 years in girls and ≥16 years in boys, annual growth of less than 2 cm) and final height was defined as the point at which the growth plates in the bone age assessment had fully closed.

Exclusion criteria were:

1) Patients with suspected NS but who did not meet the Van der Burgt (25) criteria; and,

2) Patients with confirmed diagnosis of NS but who had not yet reached final height.

Ethical approval for the study was received from Ankara University Faculty of Medicine Human Research Ethics Committee (decision no: İ10-627-22, date: 21.11.2022).

Statistical Analysis

Cases were divided into groups, stratified by male/female and those receiving GH treatment or those not receiving GH treatment. Males and females in the GH-treated and non-GH-treated groups were compared. All statistical calculations were performed using Statistical Package for the Social Sciences for Windows, version 22.0 (IBM Inc., Armonk, NY, USA). The conformity of the variables to the normal distribution was examined using visual (histogram and probability graphs) and analytical methods (Kolmogrov-Smirnov/Shapiro-Wilk test). Differences between independent groups were analyzed using the Mann-Whitney U test. Correlation analysis was performed using Spearman's method. A $p < 0.05$ was considered statistically significant.

Results

Fourteen centers participated in the study, submitting data on 67 cases, including 28 (41.8%) girls and 39 boys. In addition, the adult heights of 12 of the parents of these cases, who were diagnosed with NS, were recorded. In the evaluation of parental height and target height, affected parent were excluded. The mean age of the cases at presentation was 10.2 ± 4.1 years, with height SDS of -3.1 ± 1.1 and BMI SDS of -0.92 ± 1.3. At first presentation, 19 (28.35%) were prepubertal, and the mean bone age in all cases was 8.8 ± 3.6 years (Table 1).

All cases met the Van der Burgt (25) diagnostic criteria. In 51 of 67 (76.1%), the diagnosis was confirmed by the detection of a pathogenic variant on genetic analysis, including 43 (84.3%) in *PTPN11*, three (5.9%) in *SOS1*, two (3.9%) in *KRAS*, two (3.9%) in *RAF1*, and one (2.0%) patient had NS-related mutations in the *LZTR1* gene. Genetic analysis was not available in the remaining 16 (23.9%) patients.

The target height SDS for all cases was -1.1 ± 0.9, and there was no difference between girls (-1.2 ± 1.0) and boys (-1.0 ± 0.9) ($p = 0.25$) (Table 1).

Among the cases that reached final height, GH treatment was given to 53 cases, of whom 31 (58.5%) were boys. While the mean age at diagnosis was 10.3 ± 3.5 years, the mean age at start of GH was 11.7 ± 2.8 years. GH treatment was generally started around 1.4 years after diagnosis and follow-up continued for 5.1 ± 3.5 years. While the overall pre-treatment height SDS was -3.2 ± 1.0, the initial height SDS tended to be lower in girls (-3.7 ± 1.0 in girls vs -2.9 ± 0.9 in boys, $p = 0.02$). In cases where GH was not given, mean height SDS at diagnosis was -2.5 ± 1.2, being -3.3 SDS in girls compared to -2.0 SDS in boys (Table 2).

Table 1. Baseline characteristics of all patients with Noonan syndrome reaching final height

		Total group (n = 67)	Females (n = 28)	Males (n = 39)	p
Gender (male/female)		39/28	28	39	
Age at admission (years)		10.2 ± 4.0 11.4 [0.1; 17.0]	10.2 ± 2.9 10.5 [3.1; 13.4]	10.1 ± 4.3 11.7 [0.1; 16.5]	0.89
Puberty (yes/no)		19/48	7/21	11/28	-
Birth weight (grams)		3045 ± 707.0 3000 [1000; 4750]	2914.2 ± 689.05 3000 [1500; 4250]	3139.4 ± 714.3 3100 [1000; 4750]	0.18
Height SD at admission		-3.1 ± 1.1 -3.045 [-5.89; -0.06]	-3.6 ± 1.0 -3.565 [-5.5; -2.1]	-2.7 ± 1.0 -2.9 [-5.8; -0.01]	**0.008**
Height SD (Ranke) at admission		-0.3 ± 1.2 -0.4 [-3.1; 2.7]	-0.5 ± 1.0 -0.3 [-2.7; 0.9]	-0.2 ± 1.4 -0.5 [-3.1; 2.7]	0.07
BMI SD		-0,9 ± 1,3 -0,9 [-3.6; 2.3]	-1.1 ± 1.3 -1.0 [-3.5; 1.5]	-1.0 ± 1.5 -1.0 [-4.4; 2.3]	0.59
Bone age at admission		8.8 ± 3.6 9 [2; 18]	8.4 ± 3.9 8.8 [2; 18]	9.0 ± 3.4 10 [2; 14.6]	0.99
Target height SD		-1.1 ± 0.9 -1.1 [-2.7; 0.8]	-1.2 ± 1.0 -1.5 [-2.7; 0.8]	-1.0 ± 0.8 -1.0 [-2.5; 0.7]	0.25
Target height SD-height SD		-1.9 ± 1.1 -2.03 [-4.0; 1.7]	-2.3 ± 1 -2.1 [-3.8; -0.5]	-1.7 ± 1.1 -1.8 [-4.0; 1.7]	0.11
Growth hormone treatment (yes/no)		53/14	22/6	31/8	-
Genetic characteristics	***PTPN11***	43	18	25	-
	KRAS	2	2	0	-
	SOS1	3	3	0	-
	LZTR1	1	1	0	-
	RAF1	2	1	1	-

SD: standard deviation, BMI: body mass index

GH treatment dose ranged from 25 to 45 mcg/kg/day, with a mean of 32.9 ± 6.4 mcg/kg/day. In 29 of the cases receiving GH, the GH dose was started in the range of 25-30 mcg/kg/day, and in 24 of the cases, the dose was started in the range of 35-45 mc/kg/day. In 26 of the cases that started with the lower dose range, the dose was increased during follow-up.

When the admission characteristics of the cases receiving GH and those not receiving GH were evaluated, no difference was found in terms of age, gender, birth weight, presence of puberty, age of onset of puberty in those receiving prepubertal monitoring, target height and target height SDS. Most of the cases were prepubertal or in the early pubertal period at the time of starting GH treatment (39 were prepubertal, 12 were Tanner stage 2).

In terms of genetic characteristics of the patients receiving GH, *PTPN11* mutation was found in 36/53 (67.9%) and *KRAS* mutation was found in two (3.8%). Of the 14 cases who did not receive GH, 7 (50%) had *PTPN11*, 3 (21.4%) had *SOS1*, 2 (14.3%) had *RAF1*, and one (7.1%) had the *LZTR1* mutation. The limited number of patients with *PTPN11* made subgroup analysis unreliable.

When the growth response in the first year of follow-up was calculated as ΔHeight, this tended to be lower in those not receiving GH but this was not significantly different from those who did receive GH (Table 3).

Final Height Data

Subjects reached final height at a mean age of 17.8 ± 2.2 years. While the mean final height SDS was -2.12 ± 1.3, it was -1.96 ± 1.3 SDS in those who received GH compared to -2.7 ± 1.3 SDS in those who did not receive GH ($p = 0.84$). When data on the time of treatment discontinuation in cases receiving GH treatment was analyzed, the age at termination of GH treatment was 16.1 ± 4.4 years, and the height SDS was -2.0 ± 1.1. In these cases, there was no significant increase between the height SDS at the time of cessation of GH treatment and the final height SDS ($p > 0.05$).

When the difference between the height SDS at the start of follow-up and the final height SDS was assessed as ΔHeight SDS, this was 1.3 ± 1.1 SD in the group receiving GH and -0.2 ± 1.2 in those not receiving GH ($p < 0.001$). ΔHeight SDS (1.5 ± 1.2) in girls receiving GH and ΔHeight SDS (1.2 ± 1.2) in boys were similar ($p = 0.33$) (Figure 1). Although there was no difference between girls and boys in the group not receiving GH, the final height SDS of the boys was poorer when compared to presentation values (ΔHeight SDS in girls not given GH was 0.4 ± 0.9 and -0.6 ± 1.3 in boys, $p = 0.12$).

Table 2. Comparison of baseline characteristics of GH-treated and untreated patients

At presentation		GH-treated	GH-untreated	p
Age, (years)	Total	10.3 ± 3.5 11.4 [0.6; 16.5]	9.8 ± 5.8 11.8 [0.1; 17.0]	0.71
	Female	10.2 ± 2.9 10.5 [3.1; 13.4]	10.3 ± 5.8 11.2 [0.7; 17.0]	0.38
	Male	10.3 ± 3.8 11.7 [0.6; 16.5]	9.3 ± 6.1 11.8 [0.1; 15]	0.97
Height SDS	Total	-3.2 ± 1.0 -3.0 [-5.8; -1.4]	-2.5 ± 1.2 -2.6 [-4.5; -0.0]	0.08
	Female	-3.7 ± 1.0 -3.7 [-5.5; -2.1]	-3.2 ± 0.8 -3.0 [-4.5; -2.3]	0.20
	Male	-2.9 ± 0.9 -2.9 [-5.8; -1.4]	-2.0 ± 1.2 -1.9 [-3.7; -0.0]	0.1
Height SD (Ranke)	Total	-0.4 ± 1.2 -0.6 [-3.1; 2.7]	0.0 ± 1.1 -0.0 [-2.0; 1.7]	0.24
	Female	-0.6 ± 1.0 -0.5 [-2.7; 0.96]	-0.4 ± 1 -0.2 [-2.0; 0.6]	0.62
	Male	-0.4 ± 1.4 -0.6 [-3.1; 2.7]	0.5 ± 1.2 0.8 [-1.3; 1.7]	0.11
BMI SDS	Total	-0.8 ± 1.2 -0.9 [-3.6; 1.8]	-1.0 ± 1.6 -1.0 [-3.5; 2.3]	0.62
	Female	-1 ± 1.4 -1.0 [-2.7; 1.5]	-1.4 ± 1.2 -0.9 [-3.5; -0.4]	0.86
	Male	-0.7 ± 1.1 -0.8 [-3.6; 1.8]	-0.7 ± 1.9 -1.1 [-2.9; 2.3]	0.71
Target height SDS	Total	-1 ± 0,9 -0,8 [-2,7; 0.8]	-1.5 ± 0.8 -1.7 [-2.6; -0.3]	0.8
	Female	-1.1 ± 1.0 -1.1 [-2.7; 0.8]	-1.8 ± 1.0 -1.7 [-2.6; -0.5]	NA
	Male	-0.9 ± 0.9 -0.8 [-2.2; 0.7]	-1.36 ± 0.8 -1.3 [-2.5; -0.3]	0.25
Target height SD-height SD	Total	-2.2 ± 0.9 -2.1 [-4.0; -0.0]	-1.0 ± 1.3 -1.1 [-2.7; 1.7]	**0.002**
	Female	-2.5 ± 0.9 -2.7 [-3.8; -0.9]	-1.5 ± 0.9 -1.8 [-2.6; -0.5]	**0.06**
	Male	-2.0 ± 0.9 -2.0 [-4.0; -0.0]	-0.6 ± 1.4 -1.1 [-2.7; 1.7]	**< 0.001**
Bone age	Total	8.3 ± 3.0 8.8 [2; 13.5]	10.5 ± 5.2 12 [2; 18]	0.23
	Female	7.8 ± 2.9 8.8 [2; 12]	11.3 ± 6.4 12.7 [2; 18]	0.1
	Male	8.8 ± 3.1 9 [3; 13.5]	10.0 ± 4.6 11.5 [2; 14.6]	0.30

SDS: standard deviation (SD) score, GH: growth hormone, BMI: body mass index

Patients that reached final height were evaluated separately according to their gender. In girls the average final height and final height SDS in those using GH were 150.1 cm and -2.1 SDS, respectively. In girls who were not given GH (n = 12) the final height was 147.4 cm and final height SDS was -2.8 (p = 0.95 for height and p = 0.73 for SDS) (Table 3). ΔHeight SDS was 1.5 ± 1.2 in girls who received GH treatment and 0.4 ± 0.9 in girls who did not receive GH (p = 0.03). In terms of target height SDS, the final height-target height SDS difference (parentally adjusted height SDS) was 1.0 ± 1.4 SD in girls receiving GH treatment, while it was -1.0 ± 1.2 SD in girls not receiving GH (p = 0.008; see Table 3).

The mean final height and final height SDS in boys who reached final height and used GH were 162.4 ± 6.1 cm and -1.8 SD, respectively. The final height of boys who did not use GH was 157.4 ± 10.1 cm and final height SDS was -2.6 ± 1.4 (p = 0.34 for height and p = 0.19 for SDS). ΔHeight SDS was 1.2 ± 0.9 SDS in boys receiving GH treatment and

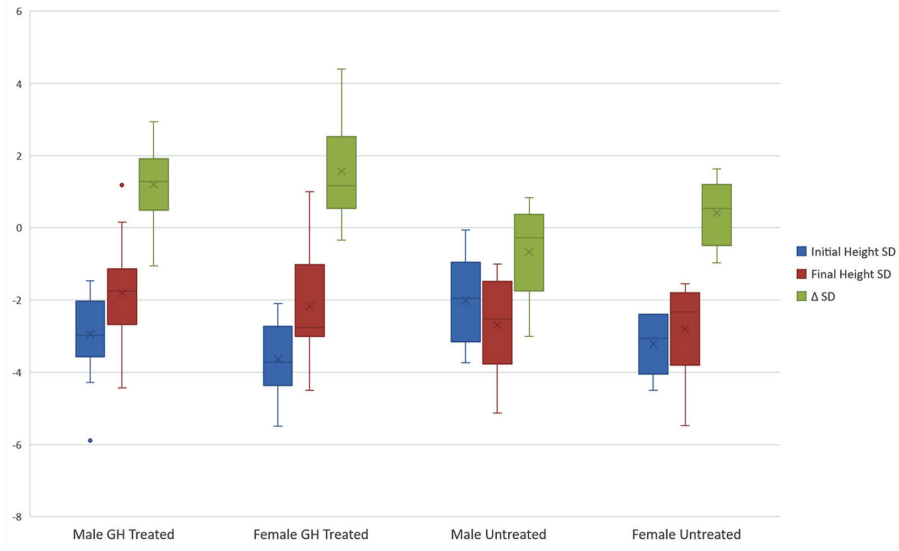

Figure 1. Initial height SDS, final height SDS, and delta height SDS of patients by GH treatment or not and gender

SDS: standard deviation score, GH: growth hormone

-0.6 ± 1.3 in those not receiving GH (p = 0.001). The final height-target height difference was 0.9 ± 1.2 SD in boys receiving GH treatment but -1.3 ± 1.6 SD in boys who did not get GH (p < 0.001; see Table 3).

In those who were started on GH, no significant correlation was found between ΔHeight SDS and age at presentation, GH, height SDS, BMI SD, bone age at presentation and also target height SDS. Again, no difference was found in terms of ΔHeight SDS between those who started GH treatment during puberty compared to those who started prepubertally (r = -0.08, p = 0.57).

For the 12 parents with NS (9 women), the mean adult height SDS was -2.2 ± 0.9 SD. The mean BMI values were 23.1 ± 1.4 kg/m^2 and BMI SDS was 0.7 ± 0.7. No additional problems were reported in the parents. The final height SDS of the subjects who did not receive treatment was similar to the height SDS of their parents who did not receive treatment (p > 0.05).

No serious side effects were observed during follow-up with GH treatment in this cohort.There were a total of 19 cases with cardiac involvement (predominantly pulmonary stenosis) who underwent corrective surgery. Eighteen of them were in the group receiving GH treatment. Hypertrophic cardiomyopathy (HCMP) was detected in two cases receiving GH treatment, and the findings during GH treatment did not change. No additional systemic findings developed during follow-up in any case. No proliferative diseases or neoplasms were reported during the follow-up period of 5.16 ± 3.54 years.

Discussion

In this multicenter study, data of children and adolescents diagnosed with NS and who reached final height were collected and analyzed. GH treatment was not initiated in all cases with NS who reached their final height. The presenting height SDSs of the cases in which GH was started tended to be worse. When treatment was started it was around 1.4 years after the diagnosis, and that the treatment dose also tended to be lower than the GH doses recommended for NS with the same dose given to the standard GH deficiency cases. Hence, the dose was increased during the follow-up. Moreover, GH was not started in some cases despite pathological short stature. Therefore, it appears that pediatric endocrinologists may have some concerns about administering GH to patients with NS. With increasing data showing that the use of GH in NS is effective and reliable, decisions can be made more easily about administering GH to cases in need.

Several studies report short- and long-term follow-up of pediatric age patients with NS and evaluate their response to GH treatment (9,10,11,13-24). After it was shown in very early studies that patients benefited from GH, including a small number of cases with NS after short-term follow-up, the results of studies with GH in long-term use in NS began to be reported (1,8,28). In studies of NS over short-term follow-up, the GH treatment dose varied between 31-66 mcg/kg/day, and there was an increase in the growth rate and height SDS of the cases. This increase was between 0.7-1.88 SDS (9,10,11,13,14,15,16,23). Data may vary in studies on final height/near final height with GH treatment.

Table 3. Comparison of final height characteristics of GH-treated and untreated patients

At last follow-up	GH-treated		GH-untreated	p
Age at final height (years)	Total	17.82 ± 2.05 17.8 [13.33; 26]	17.94 ± 2.97 17.275 [14.7; 27.3]	0.56
	Female	17.88 ± 2.66 17.91 [13.33; 26]	17.41 ± 0.78 17.37 [16.25; 18.45]	0.73
	Male	17.78 ± 1.51 17.65 [15.12; 22]	18.33 ± 3.95 17.21 [14.7; 27.3]	0.67
Final height SD (Ranke)	Total	0.56 ± 1.11 0.52 [-1.96; 2.65]	0.07 ± 1.41 0.09 [-2.1; 3.12]	0.28
	Female	0.21 ± 1.17 -0.23 [-1.49; 2.65]	-0.38 ± 1 -0.06 [-2.1; 0.63]	0.52
	Male	0.81 ± 1 0.76 [-1.96; 2.36]	0.4 ± 1.63 0.26 [-1.91; 3.12]	0.43
Final height (cm)	Total	157.34 ± 9.21 159.4 [139.3; 175]	153.16 ± 9.92 151.8 [136.2; 170]	0.27
	Female	150.1 ± 7.84 147.4 [139.3; 169]	147.43 ± 6.52 149.4 [136.2; 153.5]	0.95
	Male	162.48 ± 6.19 162.6 [145.6; 175]	157.46 ± 10.16 160.4 [140.3; 170]	0.34
Final height (SD)	Total	-1.96 ± 1.33 -1.9 [-4.5; 1.19]	-2.73 ± 1.38 -2.34 [-5.47; -1.01]	0.84
	Female	-2.1 ± 1.4 -2.76 [-3.99; 1.01]	-2.8 ± 1.44 -2.33 [-5.47; -1.55]	0.73
	Male	-1.81 ± 1.22 -1.75 [-4.43; 1.19]	-2.68 ± 1.42 -2.52 [-5.12; -1.01]	0.19
First year ΔHeight SD	Total	0.42 ± 0.61 0.49 [-2.72; 1.72]	-0.61 ± 1.23 -0.09 [-2.01; 0.28]	0.14
	Female	0.46 ± 0.41 0.56 [-0.46; 1.21]	0.28	NA
	Male	0.39 ± 0.73 0.45 [-2.72; 1.72]	-1.05 ± 1.36 -1.05 [-2.01; -0.09]	NA
Final BMI SD	Total	-1.24 ± 1.8 -1.11 [-4.9; 2.5]	-0.87 ± 1.57 -1.285 [-3.33; 2.01]	0.53
	Female	-1.12 ± 1.93 -1.15 [-4.9; 2.33]	-0.06 ± 1.66 0.45 [-2.5; 2.01]	0.24
	Male	-1.33 ± 1.74 -1.11 [-4.72; 2.5]	-1.48 ± 1.27 -1.665 [-3.33; 0.85]	0.71
Final ΔHeight SD	Total	1.36 ± 1.12 1.28 [-1.06; 4.39]	-0.2 ± 1.24 -0.07 [-3; 1.63]	**< 0.001**
	Female	1.57 ± 1.27 1.41[-0.31; 3.98]	0.41 ± 0.94 0.55 [-0.97; 1.63]	**0.03**
	Male	1.2 ± 0.98 1.28 [-1.06; 2.94]	-0.66 ± 1.3 -0.28 [-3; 0.84]	**0.001**
Target height SD-final height SD	Total	0.99 ± 1.3 1.06 [-2.73; 4.17]	-1.2 ± 1.44 -1.02 [-3.53; 0.63]	**< 0.001**
	Female	1.05 ± 1.49 1.38 [-1.84; 3.14]	-1.02 ± 1.26 -1.02 [-2.81; 0.48]	**0.008**
	Male	0.95 ± 1.2 0.89 [-2.73; 4.17]	-1.32 ± 1.61 -1.11 [-3.53; 0.63]	**< 0.001**

SD: standard deviation, BMI: body mass index, NA: not applicable

It has been reported that height gain with GH treatment was between 0.79 and 1.5 SD (17-24). In a systematic review including articles published up to 2014 in terms of adult height, the average height gain was reported to be between 0.6 and 1.4 SDS, according to national standards (29).

Looking at the data at the time of presentation, the admission height SDS value tended to be worse in those given GH treatment than in those not given GH. Although BMI, BMI SDS, bone age, and target height SDS values were not different between the groups, the difference between

height SDS and target height SDS was greater in those given GH treatment. Moreover, the height gain with GH treatment was significantly better than in those who did not receive treatment, in spite of similar ages.

In our cohort, the target height SDS was around -1.1. It can be expected that the frequency of short stature in parents of youth with NS (since they may carry the same mutation) will be significant compared to the general population. In addition, at presentation, patients with NS were approximately -2.0 SDS more negative than their parents. The height SD of the subjects in the group receiving GH was lower than the target height SD compared to the group not receiving GH. The fact that the children were shorter than their parents may have led them to present to a physician.

Patient databases created for cases receiving GH treatment are based on observational information and ensure the accumulation of sufficient data in both number and duration. In two complementary, non-interventional (NordiNet® IOS and ANSWER) studies created from these data, the safety of recombinant human GH (rhGH) treatment in 412 patients and its effectiveness in 84 patients were evaluated. The mean height SDS of the cases was -2.76, and the mean administered GH dose was 41.6 µg/kg/day. The increase in height SDS was positive with 0.49 SD at the end of the first year, 0.79 SD at the end of the second year, and 1.01 SD at the end of the third year. In the 24 cases that reached near final height [165.61 cm (-1.79 SD) in men, 154.9 cm (-1.51 SD) in women] 70.8% of them were -2 SD or above (23). In the present study, a similar proportion (67%) of the GH-treated patients achieved a height SDS of -2 SD or above. However, the final height SDS in our cohort exhibited a wider range, (-1.96 ± 1.3), indicating that while the response to GH treatment in our cohort was effective, baseline differences, lower starting doses of GH and treatment duration may account for some variation in final height outcomes.

Within the scope of the KIGS study by Ranke et al. (21), 140 patients (74 boys/66 girls) with NS who reached near final height were evaluated. While the height SDS at the beginning of treatment was -3.8 in girls and -3.2 in boys, at the end of approximately six years of follow-up, the total height gain was 1.3 SD in girls and 1.2 SD in boys. The average rhGH dose used was 0.3 mg/kg/week in girls and 0.27 mg/kg/week in boys. In the present study the initial height SDS was similar, with a mean value of -3.1 ± 1.1 across the cohort. After approximately 6.5 years of GH treatment, the height gain observed was slightly higher, with a ΔHeight SDS of 1.3 ± 1.1 SD, indicating a comparable response to GH therapy. The GH doses used in our study were slightly lower on average but still within a similar range, which might reflect variations in treatment protocols or patient-specific factors.

Sodero et al. (7) recently evaluated 43 articles examining the effectiveness and safety of GH treatment in NS, including 3.927 patients with NS, Ages ranged from 3 to 17.5 years and clinical and genetic findings were heterogeneous. The duration of GH treatment was between one and 14 years, and the height SDS increased between 0.05 to a maximum of 3.2 SD. Most of the 43 articles reported that GH treatment helps improve target height in children or adolescents with NS. Although the range of height SDS improvement in our study was narrower than reported by Sodero et al. (7), our findings align with the overall trend that GH treatment is advantageous for height gain in young patients with NS. The variations in height SDS response across different studies may be due to differences in study design, patient demographics, and GH dosing protocols.

It has been reported that the growth response in patients with NS is better the earlier GH treatment is started and the longer it is used. The duration of GH use before puberty and the height at the time of entering puberty also affect the near-final height (1). However, in the present study, no correlation was found between GH treatment and total ΔHeight SDS or the age at which treatment started or patient pubertal status at GH initiation. Since the GH treatment dose was heterogeneous, correlation between dose and treatment response was not assessed. That the time of GH initiation in our cohort was mostly in the prepubertal or early pubertal period may have led to a lack of association with pubettal status at start of GH tretment.

In the study including twenty-five years of KIGS data, the younger the age at starting GH treatment, the better the frequency of weekly injections, birth weight and height SDS at the beginning of treatment were associated with a better response. These parameters explained 36% of the increase in growth rate in the first year of treatment. Age at starting GH treatment, growth in the first year of treatment, and gender explained 74% of the change in near-final height (21).

PTPN11 mutation was detected in the majority of the cases in our study group, and 68% of those who received GH treatment and 50% of those who did not receive GH treatment had this mutation. A small number (between one and three) of those with variants in other genes were also included in the cohort. Due to the small number of cases with variants other than in *PTPN11*, no comparison between NS-associated gene differences was attmpted.

Noordam et al. (17) in a study evaluating GH treatment in NS, reported that 22/27 (81.5%) had *PTPN11* mutation, and the average age at start of rhGH was 11 years. Before treatment, median height SDS was -2.8 compared to the healthy group and 0.0 according to NS standards. GH treatment was continued for a median of 6.4 years at a dose of 0.05 mg/kg/day and height gains were +1.3 SDS according to the standard height SDS and +1.3 according to the NS standard. The average adult height for males was 171.3 cm (median, 171.6), and the average adult height for females was 157.3 cm (median, 156.4 cm). No difference in height gain was observed in the group with *PTPN11* mutation compared to those without mutation. In our study, the baseline height SDS of patients who received GH treatment was lower (-3.2 ± 1.0), with the age of GH initiation being similar. However, in contrast to Noordam et al. (17), we observed a significant improvement in height SDS in our cohort, with a ΔHeight SDS of 1.3 ± 1.1 SD in those who received GH, compared to -0.2 ± 1.2 SD in those who did not. The height gain in our study appears to be in line with the findings of Noordam et al. (17), though the baseline SDS in our cohort was poorer, indicating a greater deficit before treatment.

It has been suggested that the severity of clinical phenotype is not important in terms of response to GH treatment. However, the relationship between genotype and growth response has been investigated and it has been suggested that cases with *PTPN11* mutation, especially, may have less growth response. In some short-term studies with a limited number of cases, it has been reported that the growth response of cases with *PTPN11* mutation may be less than that of those without *PTPN11* mutation (10,30). However, this findings was not replicated in other larger and longer-term studies (9,13,21,31). Since the cases were treated with different protocols, the answers regarding the effectiveness of the treatment are still controversial.

In patients who received GH treatment, GH treatment was discontinued when puberty was completed and the epiphyses closed. Thus, there was no increase in height after GH was discontinued. In our cases, height SDS at the time of discontinuation of GH treatment and final height SDS were not different. So, we conclude that GH was given for a sufficient period in our cohort. It is known that in NS, growth may continue until later than normal due to features of pubertal progress specific to NS. The growth spurt occurs with a delay of about 2 years compared to normal children, which leads to prolonged catch-up growth at the end of the second decade of life. However, peak height velocity is low and lower than that in normal-timed puberty (6,32). Therefore, it is important to monitor NS patients treated with GH until puberty is completed.

Different side effects have been reported with GH treatment in patients with NS. Since the underlying pathology in patients with NS is an increase in the Ras/MAPK signaling pathway, it has been reported that the occurrence of benign and malignant proliferative diseases may be higher, independent of GH treatment (33). No neoplasia was found in our cases with long-term follow-up. Although there is an increased risk in the nature of the disease, it has been stated that there is no additional increase in the frequency of malignancy in cases receiving GH treatment, and serious side effects rarely develop (21,23).

In our case series, HCMP was observed in two cases receiving GH treatment, which remained stable and did not lead to cessation of treatment. Due to the presence of structural cardiac deffects and the development of HCMP in patients with NS, questions have arisen regarding the risk of rhGH treatment that may increase the frequency of cardiac side effects. The effect of GH treatment on the heart have been studied in different studies. Data generally support that the frequency or severity of HCMP does not increase with GH treatment in patients with NS (11,26,34,35,36). In a study that included a large database, cardiac side effects were identified in only seven of 429 children with NS who received rhGH, and it was reported that there was no relationship between these cardiac events and GH treatment (14).

In the present study two patients had *RAF1* mutation and both were in the group that did not receive GH treatment. Since ventricular hypertrophy is progressive, especially in NS with *RAF1* mutation, it should be remembered that caution should be exercised regarding GH treatment (36).

Study Limitations

The strengths of the present study include having two homogeneous groups with long follow-up and so patients who did and those who did not receive GH treatment were evaluated and compared However, limitations of the present study include genetic mutation analysis not being performed in all cases. Since the number of patients with mutations in genes other than *PTPN11* was small, no comparison was attempted. Indications for dosage of GH therapy were not uniform due to data being collected retrospectively from different centers using no standardized treatment protocol for GH in NS.

Conclusion

There was a better height gain with GH treatment in patients with NS who reached their final height, compared to those who did not receive GH. Early presentation, starting GH therapy without delay in cases where necessary, and

having a better target height SDS may be associated with a better GH treatment effect. Finally, it should be noted that there were no additional adverse effects seen during GH treatment which should reassure clinicians managing NS that GH treatment in these patients is safe.

Ethics

Ethics Committee Approval: Ethical approval for the study was received from Ankara University Faculty of Medicine Human Research Ethics Committee (decision no: İ10-627-22, date: 21.11.2022).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

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Conflict of Interest: Four authors of this article, Serap Turan, Korcan Demir, Abdullah Bereket and Feyza Darendeliler, are a members of the Editorial Board of the Journal of Clinical Research in Pediatric Endocrinology. However, they did not involved in any stage of the editorial decision of the manuscript. The other authors declared no conflict of interest.

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References

1. Rodríguez F, Gaete X, Cassorla F. Etiology and treatment of growth delay in Noonan syndrome. Front Endocrinol (Lausanne). 2021;12:691240.
2. De Rocca Serra-Nédélec A, Edouard T, Tréguer K, Tajan M, Araki T, Dance M, Mus M, Montagner A, Tauber M, Salles JP, Valet P, Neel BG, Raynal P, Yart A. Noonan syndrome-causing SHP2 mutants inhibit insulin-like growth factor 1 release via growth hormone-induced ERK hyperactivation, which contributes to short stature. Proc Natl Acad Sci U S A. 2012;109:4257-4262. Epub 2012 Feb 27
3. Malaquias AC, Jorge AAL. Activation of the MAPK pathway (RASopathies) and partial growth hormone insensitivity. Mol Cell Endocrinol. 2021;519:111040. Epub 2020 Oct 1
4. Roberts AE, Allanson JE, Tartaglia M, Gelb BD. Noonan syndrome. Lancet. 2013;381:333-342. Epub 2013 Jan 10
5. Croonen EA, Draaisma JMT, van der Burgt I, Roeleveld N, Noordam C. First-year growth in children with Noonan syndrome: Associated with feeding problems? Am J Med Genet A. 2018;176:951-958.
6. Edouard T, Zenker M, Östman-Smith I, Ortega Castelló E, Wolf CM, Burkitt-Wright E, Verloes A, García-Miñaúr S, Tartaglia M, Shaikh G, Lebl J. Management of growth failure and other endocrine aspects in patients with Noonan syndrome across Europe: A sub-analysis of a European clinical practice survey. Eur J Med Genet. 2022;65:104404. Epub 2021 Dec 9
7. Sodero G, Cipolla C, Pane LC, Sessa L, Malavolta E, Arzilli F, Leoni C, Zampino G, Rigante D. Efficacy and safety of growth hormone therapy in children with Noonan syndrome. Growth Horm IGF Res. 2023;69-70:101532. Epub 2023 Apr 9
8. Binder G. Noonan syndrome, the Ras-MAPK signalling pathway and short stature. Horm Res. 2009;71(Suppl 2):64-70. Epub 2009 Apr 29
9. Şıklar Z, Genens M, Poyrazoğlu Ş, Baş F, Darendeliler F, Bundak R, Aycan Z, Savaş Erdeve Ş, Çetinkaya S, Güven A, Abalı S, Atay Z, Turan S, Kara C, Can Yılmaz G, Akyürek N, Abacı A, Çelmeli G, Sarı E, Bolu S, Korkmaz HA, Şimşek E, Çatlı G, Büyükinan M, Çayır A, Evliyaoğlu O, İşgüven P, Özgen T, Hatipoğlu N, Elhan AH, Berberoğlu M. The growth characteristics of patients with Noonan syndrome: results of three years of growth hormone treatment: a nationwide multicenter study. J Clin Res Pediatr Endocrinol. 2016;8:305-312. Epub 2016 Apr 29
10. Limal JM, Parfait B, Cabrol S, Bonnet D, Leheup B, Lyonnet S, Vidaud M, Le Bouc Y. Noonan syndrome: relationships between genotype, growth, and growth factors. J Clin Endocrinol Metab. 2006;91:300-306. Epub 2005 Nov 1
11. MacFarlane CE, Brown DC, Johnston LB, Patton MA, Dunger DB, Savage MO, McKenna WJ, Kelnar CJ. Growth hormone therapy and growth in children with Noonan's syndrome: results of 3 years' follow-up. J Clin Endocrinol Metab. 2001;86:1953-1956.
12. Horikawa R, Ogata T, Matsubara Y, Yokoya S, Ogawa Y, Nishijima K, Endo T, Ozono K. Long-term efficacy and safety of two doses of Norditropin® (somatropin) in Noonan syndrome: a 4-year randomized, double-blind, multicenter trial in Japanese patients. Endocr J. 2020;67:803-818. Epub 2020 May 9
13. Romano AA, Blethen SL, Dana K, Noto RA. Growth hormone treatment in Noonan syndrome: the National Cooperative Growth Study experience. J Pediatr. 1996;128:18-21.
14. Lee PA, Ross J, Germak JA, Gut R. Effect of 4 years of growth hormone therapy in children with Noonan syndrome in the American Norditropin Studies: Web-Enabled Research (ANSWER) Program® registry. Int J Pediatr Endocrinol. 2012;2012:15.
15. Apperley LJ, Ramakrishnan R, Dharmaraj P, Das U, Didi M, Blair J, Senniappan S. Effect of growth hormone therapy in patients with

Noonan syndrome: a retrospective study. Int J Endocrinol Metab. 2020;18:e107292.

16. Osio D, Dahlgren J, Wikland KA, Westphal O. Improved final height with long-term growth hormone treatment in Noonan syndrome. Acta Paediatr. 2005;94:1232-1237.
17. Noordam C, Peer PG, Francois I, De Schepper J, van den Burgt I, Otten BJ. Long-term GH treatment improves adult height in children with Noonan syndrome with and without mutations in protein tyrosine phosphatase, non-receptor-type 11. Eur J Endocrinol. 2008;159:203-208. Epub 2008 Jun 18
18. Kirk JM, Betts PR, Butler GE, Donaldson MD, Dunger DB, Johnston DI, Kelnar CJ, Price DA, Wilton P, Group tU. Short stature in Noonan syndrome: response to growth hormone therapy. Arch Dis Child. 2001;84:440-443.
19. Otten BJ, Noordam K. Short stature in Noonan Syndrome: Results of growth hormone treatment in KIGS. In: Ranke MB, Price DA, Reiter EO (eds). Growth Hormone Therapy in Pediatrics - 20 Years of KIGS. Basel, Karger, 2007;347-355.
20. Romano AA, Dana K, Bakker B, Davis DA, Hunold JJ, Jacobs J, Lippe B. Growth response, near-adult height, and patterns of growth and puberty in patients with Noonan syndrome treated with growth hormone. J Clin Endocrinol Metab. 2009;94:2338-2344. Epub 2009 Apr 28
21. Ranke MB, Lindberg A, Carlsson M, Camacho-Hübner C, Rooman R. Treatment with growth hormone in Noonan syndrome observed during 25 years of KIGS: near adult height and outcome prediction. Horm Res Paediatr. Horm Res Paediatr. 2019;91:46-55. Epub 2019 Apr 2
22. Malaquias AC, Noronha RM, Souza TTO, Homma TK, Funari MFA, Yamamoto GL, Silva FV, Moraes MB, Honjo RS, Kim CA, Nesi-França S, Carvalho JAR, Quedas EPS, Bertola DR, Jorge AAL. Impact of growth hormone therapy on adult height in patients with PTPN11 mutations related to Noonan syndrome. Horm Res Paediatr. 2019;91:252-261. Epub 2019 May 27
23. Rohrer TR, Abuzzahab J, Backeljauw P, Birkegård AC, Blair J, Dahlgren J, Júlíusson PB, Ostrow V, Pietropoli A, Polak M, Romano A, Ross J, Sävendahl L, Miller BS. Long-term effectiveness and safety of childhood growth hormone treatment in Noonan syndrome. Horm Res Paediatr. 2020;93:380-395. Epub 2021 Jan 13
24. Libraro A, D'Ascanio V, Cappa M, Chiarito M, Digilio MC, Einaudi S, Grandone A, Maghnie M, Mazzanti L, Mussa A, Patti G, Scarano E, Spinuzza A, Vannelli S, Wasniewska MG, Ferrero GB, Faienza MF. Growth in children with Noonan syndrome and effects of growth hormone treatment on adult height. Front Endocrinol (Lausanne). 2021;12:761171.
25. van der Burgt I. Noonan syndrome. Orphanet J Rare Dis. 2007;2:4.
26. Neyzi O, Bundak R, Gökçay G, Günöz H, Furman A, Darendeliler F, Baş F. Reference values for weight, height, head circumference, and body mass index in Turkish children. J Clin Res Pediatr Endocrinol. 2015;7:280-293.
27. Ranke MB, Heidemann P, Knupfer C, Enders H, Schmaltz AA, Bierich JR. Noonan syndrome: growth and clinical manifestations in 144 cases. Eur J Pediatr. 1988;148:220-227.
28. van der Burgt I, Berends E, Lommen E, van Beersum S, Hamel B, Mariman E. Clinical and molecular studies in a large Dutch family with Noonan syndrome. Am J Med Genet. 1994;53:187-191.
29. Noonan JA, Kappelgaard AM. The efficacy and safety of growth hormone therapy in children with noonan syndrome: a review of the evidence. Horm Res Paediatr. 2015;83:157-166. Epub 2014 Dec 10
30. Otten BJ, Noordam C. Growth in Noonan syndrome. Horm Res. 2009;72(Suppl 2):31-35. Epub 2009 Dec 22
31. Binder G, Neuer K, Ranke MB, Wittekindt NE. PTPN11 mutations are associated with mild growth hormone resistance in individuals with Noonan syndrome. J Clin Endocrinol Metab. 2005;90:5377-5381. Epub 2005 Jun 28
32. Giacomozzi C, Deodati A, Shaikh MG, Ahmed SF, Cianfarani S. The impact of growth hormone therapy on adult height in noonan syndrome: a systematic review. Horm Res Paediatr. 2015;83:167-176. Epub 2015 Feb 21
33. Choi JH, Lee BH, Jung CW, Kim YM, Jin HY, Kim JM, Kim GH, Hwang JS, Yang SW, Lee J, Yoo HW. Response to growth hormone therapy in children with Noonan syndrome: correlation with or without PTPN11 gene mutation. Horm Res Paediatr. 2012;77:388-393.
34. Brown DC, Macfarlane CE, McKenna WJ, Patton MA, Dunger DB, Savage MO, Kelnar CJ. Growth hormone therapy in Noonan's syndrome: non-cardiomyopathic congenital heart disease does not adversely affect growth improvement. J Pediatr Endocrinol Metab. 2002;15:851-852.
35. Noordam C, Draaisma JM, van den Nieuwenhof J, van der Burgt I, Otten BJ, Daniels O. Effects of growth hormone treatment on left ventricular dimensions in children with Noonan's syndrome. Horm Res. 2001;56:110-113.
36. Seo GH, Yoo HW. Growth hormone therapy in patients with Noonan syndrome. Ann Pediatr Endocrinol Metab. 2018;23:176-181. Epub 2018 Dec 31