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Research Article

Evaluation of Growth Characteristics and Final Heights of Cases Diagnosed with Noonan Syndrome on GH Treatment

Şıklar Z et al. Growth Characteristics and Final Heights of Cases with Noonan Syndrome

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What is already known about this topic?

- Short stature is a common characteristic of Noonan Syndrome, with many individuals' adult height remaining below the 3rd percentile.
- Growth hormone (GH) treatment has been shown to be beneficial in improving height outcomes in patients with Noonan Syndrome.

What this study adds to the literature?

- This study presents national data on the efficacy and safety of GH in children and adolescents with Noonan Syndrome.
- This national study confirms that GH treatment significantly increases final height in children and adolescents with Noonan Syndrome, with a mean increase of approximately +1.4 SDS.
- GH treatment is demonstrated to be safe in patients with Noonan Syndrome, with no significant side effects observed and stable cardiac findings in those with hypertrophic cardiomyopathy.

Abstract

Introduction: Proportional short stature is one of the most important features of Noonan Syndrome, and adult height often remains below the 3rd percentile. Although the pathophysiology of short stature in NS patients is not fully understood, it has been shown that GH treatment is beneficial in NS, and it significantly improves the height in respect to the results of short and long-term GH treatment.

Methods: In this study, the efficacy of GH therapy was evaluated in children and adolescents with Noonan syndrome who attained final height. In this national cohort study, 67 cases with NS who reached final height from 14 centers were evaluated.

Results: A total of 53 cases (mean follow-up time 5.6 years) received GH treatment. Height SDS of the subjects who were started on GH tended to be shorter than those who did not receive GH (-3.26± 1.07 vs. -2.53 ±1.23) at initial presentation. The mean final height and final height SDS in girls using GH vs those not using GH were 150.1 cm and -2.17 SD vs 47.4 cm and-2.8 SD, respectively. The mean final height and final height SDS in boys using GH vs. not using GH were 162.48 ± 6.19 cm and -1.81 SD vs 157.46 ± 10.16 cm and -2.68 ± 1.42 SD, respectively. The Δheight SDS value of the cases was significantly higher in the group receiving GH than in 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 the cases during follow-up.

Conclusion: In patients with Noonan syndrome who reach their final height, a significant increase in height is observed with GH treatment, and an increase of approximately +1.4 SDS can be achieved. It has been concluded that GH treatment is safe and effective.

Keywords: Final Height, Growth hormone, Noonan syndrome, Treatment

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Introduction

Noonan Syndrome (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 Noonan Syndrome by altering protein-coding genes. In most cases, the genetic mutations that cause Noonan Syndrome are "gain-of-function" mutations and lead to RAS/MAPK hyperactivation, which causes the NS phenotype (2).

Postnatal-onset proportionate short stature is one of the main features of Noonan Syndrome and the most common reason for presentation to pediatric endocrinology clinics (1,3). The growth rate decreases in the first year of life after birth and in the first year, with a height SDS loss of 1.5 SD and weight increase loss by 2 SD (4,5). Compared to the general population, adult height in cases with NS 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 Noonan Syndrome patients is not fully understood, the cause of short stature is multifactorial, and response to growth hormone (GH) stimulation tests shows variations. Regarding GH, it is stated that there may be a deficiency, neurosecretory dysfunction, or mild GH resistance. IGF1 levels are at low normal ranges (7-9). It has been shown that GH treatmentis beneficial in Noonan Syndrome, and it significantly improves height in studies with short and long-term GH administration (7,9-24). However, questions regarding the growth in Noonan Syndrome are still open to research. Questions remain regarding the effectiveness and safety of growth hormone treatment in Noonan Syndrome. Predictive models are not yet practical as they may not be sufficiently reliable for 'target size' families. The potential genetic growth and its implications are not yet fully understood, which limits the current utility of these models. In particular, final height studies are spare and the age at last follow-up is insufficient in some, and the results are variable. There is no data on the final heights of Noonan Syndrome cases with or without GH treatment in the Turkish population.

We aimed to evaluate the efficacy of GH therapy in children and adolescents with Noonan syndrome who attained their final height. It was aimed to retrospectively evaluate the admission characteristics and final height of the cases, regardless of whether GH treatment was applied or not, and to determine the factors affecting the final height.

CASES AND METHODS:

The study was conducted in a multicenter manner, including centers that are members of the Turkish Pediatric Endocrinology and Diabetes Association. Patients who were followed up with a diagnosis of Noonan Syndrome according to genetic analysis and/or Van der Burgt criteria (25) and who had reached their final height were included. According to Van der Burgt criteria (25) : Diagnosis of Noonan Syndrome was confirmed under two conditions: either a typical facial appearance combined with one major clinical feature or two minor clinical features, or the presence of facial features suggestive of Noonan Syndrome alongside two major or three minor clinical features. Major criteria included characteristic facial dysmorphology, specific cardiac anomalies (such as pulmonary valve stenosis and unique ECG findings), short stature (below the 3rd percentile), and chest wall deformities (such as pectus carinatum or pectus excavatum). Additional major features included intellectual disability, cryptorchidism, or lymphatic dysplasia. Minor criteria included less distinct facial dysmorphology, non-major heart defects, short stature (below the 10th percentile), broad chest, and suggestive features in first-degree relatives. The study is cross-sectional and was conducted between September 2022 and January 2024. The study design was determined in the Turkish Pediatric Endocrinology and Diabetes Association "Noonan Syndrome Working Group", and centers with Pediatric Endocrinology specialists were invited to participate in the study. Centers having Noonan syndrome cases that reached their final height were selected, and the information of the cases 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. Clinical and laboratory features at presentation [typical facial appearance, cardiac findings, chest anomaly, cryptorchidism, neuromotor delay, visual findings, hematological findings, renal anomaly, laboratory findings, cardiac surgery history] were collected. Birth weight (g), family history of clinical features of NS, genetic diagnosis status, and variant details in NS were assessed. At presentation and final follow-up, age, puberty stage (Tanner staging), height (SD), Ranke height SD, BMI, BMI SD, and bone age were evaluated. Target height (cm), target height SD, the difference between target height SD and presentation height SD, age at completion of puberty, final height (cm), final height SD, the difference between target height SD and final height SD, and final bone age were recorded. For patients receiving GH treatment, additional variables included age at initiation of GH treatment, duration of GH treatment, GH treatment dose escalation, age, height (cm), height SD, at cessation of GH treatment, and GH dose (mcg/kg/day). ΔHeight SD was defiened as the difference between the height SDS at the 1st year of follow-up in those who do not receive GH and the height SDS at the time of admission, the difference between the beginning of GH treatment and the 1st year of treatment in those who receive GH.

Anthropometric measurements such as body weight (kg), height (cm), and head circumference (cm) were taken during examinations. Weight and height SD values were calculated according to Turkish children norms created by Olcay Neyzi and standard curves created by Ranke for cases with Noonan Syndrome (26,27). Growth velocity was calculated, and puberty staging was assessed according to Tanner Staging. The left wrist radiographs were evaluated using the Greulich-Pyle Atlas for bone age assessment.

Criteria for inclusion in the study:

1- Age at diagnosis is <18 years

2-Being diagnosed with Noonan Syndrome as a result of clinical (according to Van der Burgt criteria) and/or genetic analysis
3- Reaching 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:
1-Cases that do not meet the clinical van der Burgt criteria
2. Cases that have not reached final height
Statistical Analysis
All cases were divided into two groups: male/female and those receiving GH treatment/those not receiving GH treatment, and males and females in the GH-treated and non-GH-treated groups were compared. All statistical calculations were performed using SPSS for Windows version 22.0. 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 value of < 0.05 was considered statistically significant.
Ethical approval for the study was received from Ankara University Faculty of Medicine Human Research Ethics Committee under number 2022000361-4.

RESULTS

Fourteen centers participated in the study, and data was entered for a total of 67 cases (28 girls/39 boys). In addition, the final heights of 12 of the parents of these cases, who were diagnosed with Noonan syndrome, were recorded. In the evaluation of parental height and target height, affected parent were excluded. The average age of the cases at admission was 10.2 ± 4.1 years, height SDS -3.1 ± 1.1, BMI SDS -0.92 ± 1.3. At first admission, 19 cases were prepubertal, and the average bone age in all cases was 8.8± 3.6 years (Table 1).
All cases were found to be clinically compatible with van der Burgt's diagnostic criteria. In 51 of 67 cases, the diagnosis was confirmed by the detection of a pathogenic variant in genetic analysis. Of these, 43 are *PTPN11*, three are *SOS1*, two are *KRAS*, two are *RAF1*, and one is Noonan syndrome-related mutations in the *LZTR1* gene. Genetic analysis could not be performed in other cases.
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 their final height, GH treatment was given to 53 cases (31 boys, 22 girls). While the average age at diagnosis was 10.3 ± 3.5 years, the average age at onset of GH was 11.7 ± 2.8 years. GH treatment was initiated almost after 1.4 years of follow-up and continued for an average of 5.1 ± 3.5 years; while the pre-treatment height SDS was -3.2± 1.0, it was observed that the initial height SDS was lower in girls. (-3.7 ± 1.0 in girls vs -2.9 ± 0.9 in boys, p-value 0.02). In cases where GH was not given, height SDS at the diagnosis was -2.5 ±1.2 (.-3.3 SD in girls vs -2.0 SD in boys) (Table 2).
GH treatment dose ranged from 25 to 45 mcg/kg/day, with an average 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 a low dose, the dose was increased during follow-up.
When the admission characteristics of the cases receiving GH and those not receiving GH were evaluated, no statistical 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 TH SDS. Most of the cases were in the prepubertal or early pubertal period at the time of starting GH treatment (39 were prepubertal, 12 were Tanner stage 2).
Considering their genetic characteristics, *PTPN11* mutation was found in 36 of 53 cases receiving GH, and *KRAS* mutation was found in two. Of the 14 cases who did not receive GH, 7 had *PTPN11*, 3 had *SOS1*, 2 had *RAF1*, and one had *LZTR1* mutation. The limited number of patients with PTPN11 did not allow a subgroup analysis.
When the growth response in the first year of follow-up is determined as Δheight SD although we were unable to demonstrate it statistically, it was observed that it was lower in those who did not use GH treatment (Table 3).
Final height data: Subjects reached their final height at the age of 17.8 ± 2.2 years. While the mean final height SDS was -2.12 ± 1.3, it was found to be -1.96± 1.3 SDS in those who received GH and -2.7± 1.3 SDS in those who did not receive GH (p:0.84). When we look at the data at the time of treatment discontinuation in cases receiving GH treatment; the age at termination of GH treatment was 16.1 ±4.4 years, and the height SD 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 (as ΔheightSDS) was evaluated, it was seen that it was 1.3 ± 1.1 SD in the group receiving GH and -0.2 ± 1.2 in those not receiving GH. The difference between those who received GH treatment and those who did not receive it was statistically significant (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 statistical difference between girls and boys in the group not receiving GH, the final height SDS of the boys was more negative compared to the admission values (Δheight SDS in girls not given GH was 0.4 ± 0.9, -0.6 ± 1.3 in boys, p:0.12).
When the cases that reached their final height were evaluated separately according to their gender, the average final height and final height SDS in girls using GH were 150.1 cm and -2.1 SD, respectively. In girls who were not given GH (n:12), final height: 147.4 cm, final height SDS: -2.8 (p: 0.95 for height, p: 0.73 for HSDS) (Table 3). Considering the difference between height SDS at diagnosis and final height SDS (Δheight SDS), it is 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). Considering the target height SDS, the Final height-Target height SDS difference (Parentally adjusted height SDS) is 1.0 ± 1.4 SD in girls receiving GH treatment, while it is -1.0 ± 1.2 SD in girls not receiving GH, and the difference is statistically significant (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, final HSDS: -2.6 ± 1.4 (p= 0.34 for Height, p= 0.19 for HSDS). ΔHeight SDS was 1.2± 0.9 SD receiving GH treatment and -0.6± 1.3 not receiving GH (p:0.001). The final height-target height difference was 0.9 ± 1.2 SD in male subjects receiving GH treatment, and -1.3 ± 1.6 SD in males not receiving GH, and the difference was statistically significant (p<0.001) (Table 3).
In those who were started on GH, no significant correlation was found between Δheight SDS and age of admission, GH, height SDS, BMI SD, bone age at admission, and also target height SDS. Again, no difference was found in terms of Δheight SDS between those who started GH treatment at pubertal and prepubertal (rs:-0.08, p:0.57).
Considering parents with Noonan syndrome (9 women, 3 men), the mean adult height SD was -2.2±0.9 SD. The average BMI values were 23.1 ± 1.4 kg/m2 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 with GH treatment.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 there was no difference in the findings with the treatment. No additional systemic findings developed during follow-up in all cases. No proliferative diseases or neoplasms were reported during 5.16 ± 3.54 years .

DISCUSSION

In this multicenter study, the data of the cases with Noonan syndrome who reached their final height were collected, and their characteristics were evaluated with a focus on comparing those who received GH treatment to those who did not. It was observed that GH treatment was not initiated in all cases with Noonan syndrome who reached their final height. The height SDSs of the cases in which GH was started tended to be more negative; in other words, GH treatment was started in shorter cases. On average, it was observed that the treatment was started approximately 1.4 years after the diagnosis, and that the treatment dose was lower than the GH doses recommended for the cases with Noonan syndrome (the same dose given to the standard GH deficiency cases), and the dose was increased during the follow-up. Moreover,, it was observed that GH was not started in some cases despite pathological short stature. Therefore, it gives the impression that pediatric endocrinologists have some concerns about administering GH to patients with Noonan syndrome. With increasing data showing that the use of GH in Noonan syndrome is effective and reliable, decisions can be made more easily about administering GH to cases in need.

Several studies in the literature report short- and long-term follow-up of Noonan Syndrome patients and evaluate their response to GH treatment (9-11,13-24). After it was determined that the cases benefited from GH in the first studies that included a small number of cases in Noonan Syndrome and reported short-term follow-up, the results of long-term use of Noonan Syndrome case series began to be reported (1,8,28). In studies involving the results of Noonan Syndrome cases with short-term follow-up, the GH treatment dose varies between 31-66 mcg/kg/day, and it has been shown that there is an increase in the growth rate and Height SDS of the cases. This increase was found between 0.7-1.88 SD (9-11, 13-16,23). Data may vary in studies on final height/near final height with GH treatment. It has been reported that height gain with GH treatment is between 0.79 and 1.5 SD (17-24). In a systematic review examining articles published until 2014 in terms of adult height, it was stated that the average height gain was between 0.6 and 1.4, according to national standards (29).

Looking at the data at the time of admission, it was seen that the admission height SDS value tended to be more negative in those given GH treatment than in those not given GH. Although BMI, BMI SDS, bone age, and Target height SDS values were not statistically different in both groups, the difference between height SDS and target height SDS was found to be greater in those given GH treatment. In other words, at the beginning of treatment, the height SDS of Noonan Syndrome patients receiving GH is on the more negative side compared to the target height SDS. It was observed that the height gain with treatment was significantly higher than in those who did not receive treatment, which shows that GH treatment is effective.

In our cases, the target height SDS is around -1.1. It can be expected that the frequency of short stature in parents of cases with Noonan syndrome (since they may carry the same mutation) will be significant compared to the general population. Additionally, at presentation, patients with Noonan syndrome were approximately 2 SD 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 subjects were shorter than their parents may have led them to take their short stature more seriously and admit them 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 rhGH treatment in 412 patients and its effectiveness in 84 patients were evaluated. The mean height SDS of the cases was determined as -2.76, and the administered GH dose was 41.6 µg/kg/day. It was observed that the increase in height SDS was positive with 0.49 SD at the end of the 1st year, 0.79 SD at the end of the 2nd year, and 1.01 SD at the end of the 3rd year. It was determined that 24 of the cases reached near final height (165.61 cm (-1.79 SD) in men, 154.9 cm (-1.51 SD) in women), and 70.8% of them were -2 SD and above (23). In our study, 67% of the GH-treated patients achieved a height SDS of -2 SD or above, which is consistent with the findings from the NordiNet® IOS and ANSWER studies. However, the final height SDS in our cohort showed a wider range, with an average of -1.96 ± 1.3 in those treated with GH, indicating that while the response to GH treatment in our cohort was effective, baseline differences and treatment duration may account for some variation in final height outcomes.

Within the scope of the KIGS study by Ranke et al. 140 patients (74 boys /66 girls) with Noonan Syndrome 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 6 years of follow-up, it was observed that the total height gain was 1.3 SD in girls and 1.2 SD in boys. The average rhGH dose used is 0.3 mg/kg/week in girls and 0.27 mg/kg/week in boys (21). In our study (31 boys, 22 girls), the initial height SDS was similar, with a mean value of -3.1 ± 1.1 across the cohort. After an average of 6.5 years of GH treatment, the height gain observed in our study 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. recently evaluated 43 articles examining the effectiveness and safety of GH treatment in Noonan syndrome. When all articles were taken into consideration, it was determined that there were data on a total of 3927 Noonan syndrome cases, whose ages ranged from 3 to 17.5 years and whose clinical and genetic findings were heterogeneous. The authors stated that in the cases with Noonan syndrome reported in these publications, the duration of GH treatment was between 1 year and 14 years, and the height SDS increased between a minimum of 0.05 and a maximum of 3.2 SD. Most of the 43 articles included in the review emphasize that GH treatment helps improve target height in children or adolescents (7). Although the range of height SDS improvement in our study was narrower than reported by Sodero et al., our findings align with the overall trend that GH treatment is advantageous for height gain in Noonan syndrome patients. The variations in height SDS response across different studies might be due to differences in study design, patient demographics, and GH dosing protocols.

It is stated that the growth response in patients with Noonan Syndrome 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 our study, no correlation was found between GH treatment and total Δheight SDS, the age at which treatment started, pubertal status, etc. Since the GH treatment dose was heterogeneous, no correlation was examined between dose and treatment response. The fact that the time of GH initiation in our cases was mostly in the prepubertal or early pubertal period may cause it to not make a difference in terms of puberty.

In the study collected twenty-five years of KIGS data, and the younger the age at starting GH treatment; It has been reported that the better the frequency of weekly injections, birth weight and height SDS at the beginning of treatment, the better the response. These parameters can explain 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 explain 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 3) of those with other mutations existed. For this reason, a comparison of cases with *PTPN11* mutation and other mutations could not be made.

Noordam et al. in the study evaluating GH treatment, 22/27 of the cases included in the study had *PTPN11* mutation, and the average age of onset of rhGH was found to be 11 years old. Before treatment, median height SDS was found to be -2.8 compared to the healthy group and 0.0 according to Noonan Syndrome standards. GH treatment of the cases was continued for median 6.4 years at a dose of 0.05 mg/kg/day, and height gains were +1.3 according to the standard height SDS and +1.3 according to the Noonan Syndrome 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 (17). In our study, the baseline height SDS of patients who received GH treatment was lower, at -3.2 ± 1.0, with an average age of GH initiation being similar, at 11.7 ± 2.8 years. However, in contrast to Noordam et al., 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., though the baseline SDS in our cohort was more negative, indicating a greater deficit before treatment.

It is stated that whether the clinical phenotype is mild or severe is not important in terms of response to GH treatment. The relationship between genotype and growth response has been investigated in different studies. It has been suggested that cases with PTPN11 mutation, especially, may have less growth response. In some short-term studies, including 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 (10,31). However, this observation could not be demonstrated in other larger and longer-term studies (9, 13,21,32). Since the cases were treated with different protocols, the answers regarding the effectiveness of the treatment are still controversial.

In cases that received GH treatment, it was observed in all cases that GH treatment was discontinued when puberty was completed and the epiphyses closed. For this reason, it was observed that there was no increase in height after the period when 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 sufficient time in our cases. It is known that in Noonan syndrome, growth can continue until late ages due to puberty-specific features. A 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. Peak height velocity is low and also lower than that in normal-timed puberty (6,30). Therefore, it is important to monitor Noonan Syndrome patients treated with GH until the end of puberty.

Different side effects have been reported with GH treatment in patients with Noonan Syndrome. Since the underlying pathology in patients with Noonan Syndrome is an increase in the Ras/MAPK signaling pathway, it has been reported that the occurrence of benign and malignant proliferative diseases is high, 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 in different series (21,23).

In our case series, HCMP observed in 2 cases receiving GH treatment remained stable and did not cause the cessation of treatment. Because of the presence of structural cardiac effects and HCMP development in patients with Noonan Syndrome, hesitations have arisen regarding the risk of rhGH treatment increasing the frequency of cardiac side effects, and the effects 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 Noonan Syndrome (11,26,34-36). According to a study that included a large database, cardiac side effects were identified in 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).

Two cases had *RAF1* mutation and were in the group that did not receive GH treatment. Since ventricular hypertrophy is progressive, especially in Noonan Syndrome patients with *RAF1* mutation, it should be remembered that caution should be exercised regarding GH treatment (36).

Strengths of our study: having two homogeneous groups with long follow-up (those receiving and not receiving GH). Not only those who received GH, but also those who did not receive it were evaluated. Limitations: Genetic mutation analysis could not be performed in all cases. Since the number of people with other mutations was small, a comparison with those with *PTPN11* mutation could not be made.Indications for dosage of GH therapy were not uniform due to different centers.

As a result, it was determined that there was a better height gain with GH treatment in patients with Noonan syndrome who reached their final height, compared to those who did not receive GH. Early admission, starting GH use without delay in cases where necessary, and having a better target height SDS may ensure a more positive effect of the treatment. Also, there is no additional adverse effect seen during GH treatment.

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		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	-

Table 1: Baseline Characteristics of All Patients with Noonan Syndrome Reaching Final Height

Table 2: Comparison of Baseline Characteristics of GH-treated and Untreated Patients

Admission	GH-Treated		GH-Untreated	p
Age at Admission (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 SD at Admission	**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 SD	**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 SD	**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 at Admission	**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

Table 3: Comparison of Final Height Characteristics of GH-Treated and Untreated Patients

Last Control	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
1st 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**

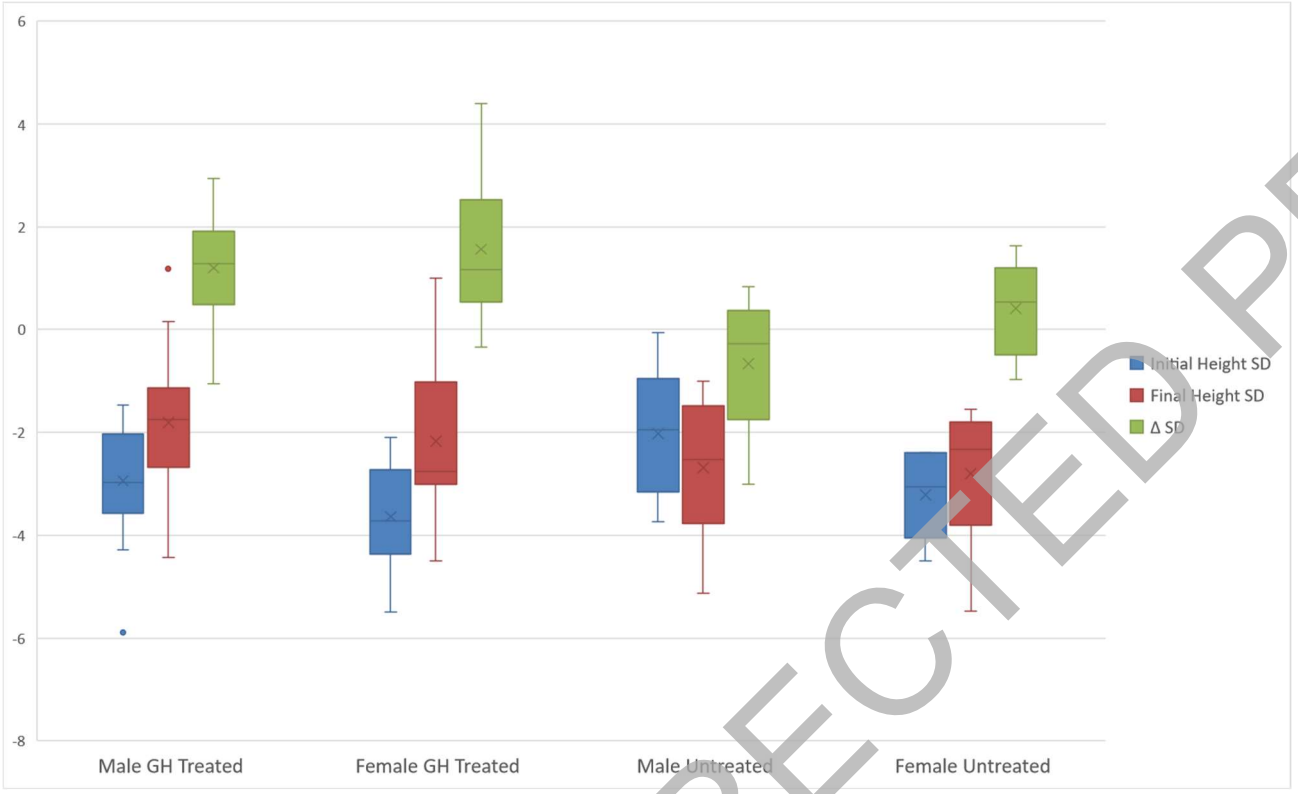

Figure 1: Initial height SD, final height SD, and delta height SD of patients according to GH treatment and gender