The Noonan syndrome (NS) is an autosomal dominant disorder that involves multiple organ systems, with short stature as the most common presentation (>70%). Possible mechanisms of short stature in NS include growth hormone (GH) deficiency, neurosecretory dysfunction, and GH resistance. Accordingly, GH therapy has been carried out for NS patients over the last three decades, and multiple studies have reported acceleration of growth velocity (GV) and increase of height standard deviation score (SDS) in both prepubertal and pubertal NS patients upon GH therapy. One year of GH therapy resulted in almost doubling of GV compared with baseline; afterwards, the increase in GV gradually decreased in the following years, showing that the effect of GH therapy wanes over time. After four years of GH therapy, ~70% of NS patients reached normal height considering their age and sex. Early initiation, long duration of GH therapy, and higher height SDS at the onset of puberty were associated with improved final height, whereas gender, dosage of GH, and the clinical severity did not show significant association with final height. Studies have reported no significant adverse events of GH therapy regarding progression of hypertrophic cardiomyopathy, alteration of metabolism, and tumor development. Therefore, GH therapy is effective for improving height and GV of NS patients; nevertheless, concerns on possible malignancy remains, which necessitates continuous monitoring of NS patients receiving GH therapy.

Keywords: Noonan syndrome, Growth hormone

Introduction

Noonan syndrome (NS) is an autosomal dominant disorder that involves multiple organ systems, with an incidence of 1:1,000 to 1:2,500. LEOPARD syndrome (OMIM 151100) (lentigines, electrocardiography conduction abnormalities, ocular hypertelorism, pulmonic stenosis, abnormal genitalia, retardation of growth, and sensory neural deafness), cardiofaciocutaneous syndrome (CFC; OMIM 115150), and Costello syndrome (CS; OMIM 218040) exhibit overlapping phenotypes with NS and are thus categorized as NS-related disorders. Gain-of function germline mutations that affect the components of the Ras-MAPK pathway are involved in the development of NS and its related disorders. Functional alterations of Ras/mitogen-activated protein kinase (MAPK) signaling pathway is implicated in growth factor-mediated cell proliferation, differentiation, survival and death. Gain-of function germline mutations that affect the components of the Ras-MAPK pathway are involved in the development of NS and its related disorders. Mutations in the PTPN11 gene are present in up to 50% of NS cases, followed by mutations in SOS1 and RAF1 in up to 20%. A small number of NS patients have been shown to carry mutations in KRAS, BRAF.
MEKI, and NRAS genes. In addition, a mutation in the SHOC2 gene was identified in patients with NS-like phenotypes and loose anagen hair. Still, causative mutations are unknown in 30%–40% of NS cases.

Short stature is a common presentation of NS that affects up to 70% of NS patients. Birth weight and height of NS patients are generally within normal range, but NS patients undergo subsequent height loss of 1–1.5 standard deviation score (SDS) within the first year. After 2 to 4 years, mean height begins to fall below the 3rd percentile until puberty due to delayed puberty and low peak height velocity. Mean final height is 152.7–154.4 cm in females and 167.4–169.2 cm in males, which is less than 1.5 height SDS compared with normal population. Thus, over the last three decades, GH therapy has been administered in NS patients, and U.S. Food and Drug Administration approved treatment with recombinant human growth hormone for NS patients in 2007.

This review describes a series of research in the field of GH therapy for NS patients as well as possible causes of short stature, short and long-term efficacy, factors affecting the response of GH therapy, and adverse events of GH therapy.

### Possible mechanisms of short stature

Different views on the GH secretory dynamics in studies reflect the heterogeneity of the clinical and genetic condition of NS. Possible mechanisms for short stature include GH deficiency, neurosecretory dysfunction, and GH resistance. Approximately 40% of NS patients showed peak GH level of less than 10 ng/mL in pharmacological provocation tests. Short children with NS showed disturbances in GH secretion such as low level of mean overnight GH concentration and unusual GH pulsatility with high trough GH concentration, suggesting neurosecretory dysfunction. NS patients with PTPN11 mutation had lower levels of insulin-like growth factor 1 (IGF-1) than those without PTPN11 mutation. These

### Table 1. Short and long-term efficacy of GH therapy in NS patients

| Study            | No. of patients (M/F) | Age at start (yr) | Height SDS at start | GH dose (mg/kg/day) | Duration of GH therapy (yr) | GV (cm/yr), P-value | Change in height SDS | Height SDS at last follow-up, P-value |
|------------------|-----------------------|-------------------|---------------------|---------------------|----------------------------|---------------------|---------------------|-------------------------------------|
| Cotterill et al. | 30 (19/11)            | 8.9±0.5           | -3.01±0.1           | 0.05                | 1                         | 4.9±0.2 to 8.1±0.4, <0.001 | N/A                 | -2.36±0.1, <0.001                  |
| Binder et al.    | 29 (19/10)            | Mut +:16          | 7.4±2.2             | -3.5±0.7            | 0.042±0.007               | 1                   | 0.66±0.21, -2.4±0.8             |
|                 |                       | Mut -:13          | 6.3±1.9             | -3.8±0.1            | 0.050±0.008               | N/A                 | 1.26±0.36, -2.5±1.6             |
| Choi et al.      | 18 (14/4)             | Mut +:10          | 8.3±2.4             | -2.8±0.9            | 0.066                     | 1                   | 3.6±1.6, N/A                     |
|                 |                       | Mut -:8           |                     |                     |                           |                     | 3.8±0.8, N/A                     |
| Limal et al.     | 35 (19/16)            | 10.4±3.1          | -3.3±0.9            | 0.030-0.046         | 2                         | Before: 4.7±1.1          | N/A                 | -1.9±0.9, <0.001                  |
| MacFarlane et al.| 23 (16/7)             | 9.3±2.6           | -2.7±0.4            | 0.05                | 3                         | Before: 4.2±1.7         | N/A                 | -1.5±1.2, 0.001                  |
|                 |                       | Mut +:7           | 12.9±4              | -3.6±0.1            | 0.048±0.005               | 3                   | 5.8±1.8, N/A                     |
|                 |                       | Mut -:7           | 11.7±3              | 3.4±0.1             | 0.046±0.07                | N/A                 | 3.8±0.3, 0.003                  |
| Ferreira et al.  | 14 (10/4)             | -                 |                     | 0.048±0.005         | 3                         | N/A                 | 0.76±0.41, 1.74±0.10            |
| Raaijmakers et al.| 402                   | 9.7               | -2.86               | 0.034               | 3                         | 5.8±1.5              | N/A                 | -1.2±1.0, 0.001                  |
| Jeong et al.     | 15 (11/4)             | 7.9±1.8           | -2.6±0.6            | 0.050–0.075         | 3                         | Before: 4.5±0.8         | N/A                 | -1.5±1.2, 0.001                  |
|                 |                       | Mut +:7           | 12.9±4              | -3.6±0.1            | 0.048±0.005               | 3                   | 5.8±1.5, N/A                     |
|                 |                       | Mut -:7           | 11.7±3              | 3.4±0.1             | 0.046±0.07                | N/A                 | 3.8±0.3, 0.003                  |
| Noordam et al.   | 29 (21/8)             | 11.0              | -2.8                | 0.035               | 6.4 (3 to 10)             | 1.3                 | -1.5 (-3.0 to -0.3), <0.001     |
| Romano et al.    | 65 (35/30)            | 11.6±3.0          | -3.5±1.0            | 0.33±0.05           | 5.6±2.6                   | 1.4±0.7              | -2.1±1.0, 0.001                 |
| Lee et al.       | 120                   | 9.2±1.8           | -2.7±0.7            | 0.047±0.011         | 4                         | N/A                 | -1.3±1.1, 0.001                 |
| Osio et al.      | 25 (12/13)            | 8.2±3.0           | -2.9±0.4            | 0.33–0.66           | 1–9                       | 1.7±0.9              | -1.2±1.0, 0.001                 |

Values are presented as mean±standard deviation unless otherwise indicated. Mut +, positive for mutation of PTPN11; Mut-, negative for mutation of PTPN11; GH, growth hormone; GV, growth velocity; SDS, standard deviation score; N/A, not available.
findings provide ground for the efficacy of GH therapy in the management of short stature in NS patients. Furthermore, NS patients with PTEN mutation showed impaired production of IGF-1 and acid-labile subunit with normal insulin-like growth factor binding protein 3 (IGFBP-3) levels, which can result in GH post-receptor signaling defect. 19)

Efficacy of growth hormone therapy for the height

Table 1 describes the results of previous studies on GH therapy in NS patients. Several studies have reported acceleration of growth velocity (GV) and increase in height SDS within the first year of GH therapy. About 80% of patients treated with GH (0.045 mg/kg/day) for 1 year showed significant increases in mean height SDS (-3.01±0.1 to -2.36±0.1) and height velocity (4.9±0.2 to 8.1±0.4 cm/yr). 20) Another study reported that after 1 year of GH therapy (0.066 mg/kg/day), mean height SDS and GV increased from -2.8±0.9 to -2.0±0.9 and from 5.0±0.9 to 8.9±1.6 cm/yr, respectively. 20) Furthermore, in both prepubertal and pubertal patients, mean height SDS was improved after one year of GH therapy. 19)

After 3 years of GH therapy (0.05–0.075 mg/kg/day), significant increases in height SDS and GV were observed. 22,23) GV was the highest during the first year of treatment and gradually decreased every year thereafter, showing that GH therapy effectiveness wanes over time. 21,22) Approximately 78% of patients showed increased GV of more than 2 cm/yr during the first year, which decreased to 52.2% and 30.4% in the second and third years, respectively. 22) Similarly, another study reported a significant acceleration in GV, in which GV almost doubled after the first year of GH therapy compared with GV at baseline, followed by gradual decrease in the following years. 21) The decreasing trend of gain in height SDS for years 2 and three of GH therapy was not related to poor adherence to therapy, and persisted even upon yearly increases in the mean dosage of GH therapy. 22,23) The waning of GH therapy effect in NS patients may be due to age at the beginning of GH therapy, GH secretory status, GH resistance, and genetic factors.

Similarly, height SDS also increased from -2.6 to -1.3 upon 4 years of GH therapy, and about 70% of 17 patients reached normal height range considering age and sex (height SDS > -2). 24) Patients who were treated with GH for more than 3 years (median, 6.4 years) showed increase of 1.3 height SDS; consequently, 22 out of 29 patients achieved adult height within normal range. 20) However, even after 4 years of GH therapy, 29% of patients remained less than -2 height SDS. 24) Such differences in the effect of GH therapy might be due to resistance to GH or advanced bone age relative to chronologic age at the beginning of GH therapy.

Most patients given GH therapy (0.33 mg/kg/day) showed substantial gain in final height, with SDS ranges from 1.4 to 1.7. 26,27) Males showed 10.9±4.9 cm growth while females showed 9.2±4.0 cm by the age of 18 years. 26,27) In 60% of patients, mean adult height reached 157.7 cm in females and 174.5 cm in males. 27) Without GH therapy, all males or females with less than -2 height SDS did not show any noticeable catching up in growth after onset of puberty. 26) However, additional spontaneous height gains of 1.00 SDS and 0.57 SDS were observed in mid-to-late female teenagers and males in early 20s, respectively, which may be associated with delayed puberty. 13)

In fact, mean final height of GH-untreated patients reached 154.4 cm (-1.73 SDS) for females and 169.2 cm (-1.27 SDS) for males. 14) Therefore, pubertal growth spurt that present much later than expected should be taken into consideration for assessment of the efficacy of GH therapy in terms of final height.

GH therapy was associated with advancement of bone age of 1.1–1.2 years/yr. 25,26,27) Mean difference between chronological age and bone age decreased and bone maturity score increased after one year of GH therapy. 20) As the bone age was more delayed at the start of GH therapy, the advancement of bone age underwent faster acceleration after GH therapy. 13) There was a negative correlation between bone age at the start of GH therapy and one-year height SDS. 20) Among NS patients who received GH therapy, those who showed significant increase in adult height did not have excessively advanced bone age. 22,23) Because NS patients typically begin GH therapy with markedly delayed bone age, the advancement of bone age during GH therapy may reflect normalization rather than excessive acceleration of bone age.

Factors affecting response of GH therapy

As the age at the onset of puberty is a predictive factor for adult height, delayed onset of puberty has a positive effect on treatment response. 25) Earlier initiation of GH therapy has an impact on the changes in height SDS after 1 and 2 years of treatment. 25,27) In particular, when using the age of 11 years in male and 10 years in female as a cutoff for younger versus older age, patients who started GH therapy at a younger age showed a trend of higher gain in change to height SDS after 1 year and 2 years of treatment. 26) Duration of GH therapy at prepubertal period and height SDS at the onset of puberty were also positively correlated with the increment in prepubertal height SDS and near-adult height SDS, respectively. 25,26) In summary, early initiation and long duration of GH therapy as well as higher height SDS at the onset of puberty are correlated with taller final height.

The mean gain in height SDS was similar for males and females during up to 2 years of GH therapy, suggesting that gender does not significantly affect the efficacy of GH therapy. 25) Additionally, there is no significant beneficial effect of higher dosage for final height, as demonstrated by previous studies that used different doses of GH (0.33–0.66 mg/kg/day). 25,27,28) Basal IGF-1 and IGFBP-3 before GH therapy were significantly related to height and GV, and subsequent improvements in IGF-1 and IGFBP-3 level after one year of GH treatment were related to increases in height velocity. 17) Other studies showed also serum IGF-1 and IGFBP-3 level increased after 1 year of therapy. 21,25) However, basal IGF-1 and IGFBP-3 level could not
Adverse events of growth hormone therapy

Several studies have shown that blood glucose levels remain within normal ranges during GH therapy.22,25,27 In addition, there were no abnormalities in metabolic profiles including HbA1c, triglyceride, and cholesterol over three years of GH therapy.22 There was no evidence of excess ventricular wall thickness upon 1 year of GH therapy (0.05 mg/kg/day).20 Prospective GH trials of over 3 years showed that no children with NS experienced any serious complication of heart based on echocardiography.27 In particular, there were no significant thickening in left ventricular dimensions between 27 children with NS given GH (0.05 mg/kg/day) and 16 NS controls.21 For longer duration (mean, 5.6 years) of GH therapy, there was no significant change in ventricular wall thickness.25 Two patients showed mild progression of pulmonary valve stenosis, but it was not considered to be related to GH therapy.25 Two out of 65 patients presented biventricular hypertrophy and hypertrophic cardiomyopathy, which were manifestations of NS.20 Despite such positive outcomes, GH therapy in patients with RAF1 mutation is controversial because ventricular hypertrophy may have progressive course. Thus, careful monitoring is recommended to detect any possible hypertrophic cardiomyopathy and progression of the underlying heart disease during GH therapy.

NS confers increased risk of benign and malignant proliferative conditions ranging from hematological abnormalities to solid tumors.2,22 Patients with PTPN11 mutations had 3.5-times higher overall cancer risk by age of 55 years compared to general population.32 NS is often associated with dysembryoplastic neuroepithelial tumor of the brain, and GH therapy should be carried out with caution because it may promote tumor growth.30 In 1 patient with a previous diagnosis of maxillary germ cell granuloma, recurrence of the mandible was observed upon GH therapy,26 whereas another patient was able to start GH treatment again after lymphoma remission.27 There is a lack of follow-up studies on the risk of tumor development and its recurrence in large or small cohorts of NS patients treated with GH. Thus, all NS patients who undergo GH therapy should be evaluated for the association between malignancy risk and GH therapy.

This review suggested regular follow-up tests for prevention or early detection of adverse events of GH therapy based on the evaluation performed at this center (Table 2).

Conclusions

GH therapy in NS patients is effective for improving height and GV, enabling them to reach normal final height regardless of clinical severity and genotype. Early initiation (especially in the prepubertal period) and long duration of GH therapy predict changes in height SDS.21,24 Notably, NS patients showed similar response to GH therapy regardless of the severity of clinical phenotype.26 There was small difference in the increase of height SDS in both severe and moderate NS subgroups after 2 years of GH therapy (0.05 mg/kg/day) despite the higher GH secretion in the severe subgroup.26

Studies on the severity of short stature and response to GH therapy according to the existence of mutation have shown conflicting results. Some studies reported a tendency to better response of height SDS from one to 3 years of GH therapy in patients without PTPN11 mutations.18,19,23,30 However, others showed contradictory results in that response to GH therapy was not significantly different between patients with PTPN11 mutations and those without.21,23 In addition, IGF-1 and IGFBP-3 levels at the start of GH therapy were significantly lower in patients with PTPN11 mutation, which suggest mild GH resistance in mutation-positive patients.30 However, response to GH therapy represented by changes in serum IGF-1 and IGFBP-3 levels was not significantly different according to the presence of mutation.21,25

Table 2. Proposed regular follow-up tests for prevention or early detection of adverse events of GH therapy

| Evaluation        | Test                                      | Comments                                      |
|-------------------|-------------------------------------------|-----------------------------------------------|
| Initial evaluation| CBC, creatinine, LFT, fasting glucose, cholesterol, HbA1c, TSH, free T4, IGF-1, IGFBP3, echocardiography, ECG | Every 3 months if serum fasting blood glucose level is > 126 mg/dL in 2 consecutive tests, HbA1c is recommended |
| Routine evaluation| CBC, creatinine, LFT, fasting glucose, cholesterol | Every 3 months | |
| Endocrine evaluation| TSH, free T4, IGF-1, IGFBP3, Bone age | Every 3 months | Every 6 months |
| Cardiac evaluation| Echocardiography, ECG | Not recommend regular follow-up if ventricular hypertrophy or congenital heart defect was presented in previous examination, recommend evaluate every 1–2 years |
| Tumor evaluation | Not recommend regular follow-up if symptom present, evaluate by each system |

GH, growth hormone; CBC, complete blood count; LFT, liver function test; HbA1c, hemoglobin A1c; TSH, thyroid stimulating hormone; IGF-1, insulin-like growth factor 1; IGFBP3, insulin-like growth factor binding protein 3; ECG, electrocardiogram.
show positive effect on final height. These results emphasize the importance of early diagnosis and initiation of GH therapy for optimal height outcomes. Furthermore, even though evidence on adverse events due to GH therapy in NS patients is scarce, careful monitoring of cardiac changes and malignancy is desired.

**Conflict of interest**

No potential conflict of interest relevant to this article was reported.

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