Response to Growth Hormone Therapy in Children with Noonan Syndrome: Correlation with or without *PTPN11* Gene Mutation

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Key Words

Growth hormone · Noonan syndrome · *PTPN11*

Abstract

Background/Aims: The objective of this study was to evaluate the efficacy of recombinant human growth hormone (rhGH) therapy and the influence of genotype on the response to rhGH therapy in children with Noonan syndrome (NS). **Methods:** 14 male and 4 female subjects with NS with short stature, whose height was <3rd percentile, were included. The rhGH was subcutaneously administered at a dose of 66 µg/kg/day. Mutations in the *PTPN11* gene were identified in 10 subjects (55.6%). Mutations in the *SOS1* (2 children, 11.1%), *MEK1* (1 child, 5.6%) and *KRAS* (1 child, 5.6%) genes were also found. **Results:** Height SDS increased from -2.8 ± 0.9 at the start of rhGH therapy to -2.0 ± 0.9 12 months later ($p < 0.001$). Height velocity increased from 5.0 ± 0.9 cm/year in the year before treatment to 8.9 ± 1.6 during treatment ($p < 0.001$). Changes in height SDS, height velocity, and serum IGF-1 level did not differ significantly between those children with or without *PTPN11* mutations.

Conclusion: The rhGH therapy significantly improved the growth velocity and increased the serum IGF-1 level. Long-term correlation between genotype and rhGH therapy responsiveness needs to be addressed in a large population.

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Introduction

Noonan syndrome (NS) (MIM 163950) is an autosomal dominant disorder affecting 1 in 1,000–2,500 live births [1]. NS is characterized by postnatal short stature, congenital heart disease, early feeding difficulties, mild learning disabilities, and characteristic facial dysmorphisms, short and webbed neck, and chest deformities [2].

The molecular genetic pathogenesis of NS is related to functional alterations of the Ras-mitogen-activated protein kinase (MAPK) signaling pathway, which is implicated in growth factor-mediated cell proliferation, differentiation, and apoptosis. With more causative genes identified, the genotypic and phenotypic heterogeneities emerge as complex and overlapped. *PTPN11* (40–50%),

SOS1 (10–20%), and *RAF1* (3–17%) mutations are common in children with NS. A small number of patients with NS can also have *KRAS*, *BRAF*, *MEK1*, or *NRAS* mutations [3].

Proportionate short stature is well recognized as one of the key features of NS and has been reported in more than 80% of patients affected by NS [1, 4]. There are several reports from a recombinant human growth hormone (rhGH) registry, the KIGS International Growth Database [5, 6], as well as several, observational studies reporting the effects of rhGH on the near-adult height of subjects with NS [7–9]. Although these studies involved small numbers of patients with various enrollment ages, treatment durations, rhGH doses, and treatment response, rhGH therapy for NS has been reported to be effective to improve both the height velocity and the final adult height. The National Cooperative Growth Study (NCGS), a postmarketing observational study of rhGH-treated children, showed that rhGH significantly improved height SDS in relatively large numbers of children with NS [10]. In May 2007, NovoNordisk obtained FDA approval for the treatment of NS with their rhGH preparation, nortitropin using a dose of 66 µg/kg/day [11].

This study was performed to evaluate the efficacy and safety of rhGH therapy and to evaluate the influence of genotype in response to rhGH therapy in children with NS.

Subjects and Methods

Subjects

Fourteen male and 5 female study subjects with NS with short stature, whose height was <3rd percentile, were enrolled in this study. The diagnosis of NS was established clinically by a clinical geneticist experienced with NS on the basis of the van der Burgt criteria [12]. Subjects were eligible to be included in the study only if they meet all of the following criteria: age 4–15 years; prepubertal status, i.e. an absence of breast development in females and a testicular volume <4 ml in males; height ≤3rd percentile; annual growth velocity >4 cm, and naive to rhGH therapy. Children with any of the following were excluded from the study: the presence of one or more pituitary hormone deficiencies; primary hypothyroidism; adrenal insufficiency; hypogonadism; diabetes; chromosomal anomaly; hypertrophic cardiomyopathy; pregnancy, and treatment with any rhGH during the past 1 year. This study protocol was approved by the Institutional Review Board of Asan Medical Center, and written informed consent was obtained from all study subjects or from their parents.

Molecular Analyses

Genomic DNA was extracted from peripheral blood leukocytes using Puregene DNA isolation kits (Gentra, Minneapolis, Minn., USA). The coding regions and flanking intergenic se-

quences of the *PTPN11* (whole exons), *SOS1* (whole exons), *KRAS* (exon 1 and 4), *RAF1* (exon 7, 14, and 17), *SHOC2* (exon 1), and *NRAS* (exon 3) were analyzed using an ABI3130xl Genetic Analyzer (Applied Biosystems, Foster City, Calif., USA).

Study Protocol

This study was an open-labeled, non-randomized, non-interventional, observational study. Anthropometric data (height and weight) was measured by experienced observers at both the baseline and at 3-month intervals using standard anthropometric techniques. Subjects' height and weight were expressed as SDS based on normative data from Korean references [13].

Blood sampling for biochemical analysis, i.e. blood counts, routine biochemistry, fasting glucose levels, HbA1c, thyroid functions including free T₄, thyroid-stimulating hormone (TSH), insulin-like growth factor 1 (IGF-1), and IGF-binding protein 3 (IGFBP-3), were carried out at baseline and every 3 months. Serum IGF-1 levels were measured via immunoradiometric assay (IRMA) (Immunotech, Marseille, France) with inter- and intra-assay coefficients of variations (CVs) less than 6.8 and 6.3%, respectively. Serum IGFBP-3 levels were determined using a commercially available IRMA kit (Immunotech) with inter- and intra-assay CVs less than 9.5 and 6.0%, respectively. IGF-1 SDS and IGFBP-3 SDS were calculated based on normative data from Korean references [14]. The subject's bone age was determined using the Greulich-Pyle method [15]. Echocardiography was performed at the baseline and every 6 months. The rhGH (Norditropin®; Novo Nordisk Pharma, Hellerup, Denmark) was administered at a dose of 66 µg/kg/day, subcutaneously for a 12-month period.

Safety

Investigators were required to report non-serious adverse events (AE) or serious AE (SAE) reports describing any event potentially related to rhGH. SAEs are defined as events that are fatal or life-threatening, require hospitalization, result in disability, necessitate surgical intervention, and/or result in a congenital anomaly or birth defect.

Statistical Analysis

Data are expressed as the mean ± SDS and range, unless indicated otherwise. The Wilcoxon signed rank test (SPSS for Windows, version 14.0; SPSS Inc., Chicago, Ill., USA) was used for the comparison of longitudinal data. Differences between genotypes of subjects were assessed using the Mann-Whitney U test. Relationships between variables expressing growth parameters, such as chronologic age, bone age at the start of treatment, mid-parental height, and initial serum IGF-1 and IGFBP-3 levels, as well as height outcome variables including height SDS and growth velocity, were assessed using the Spearman rank correlation. A test result was considered to be statistically significant if $p < 0.05$.

Results

Clinical Characteristics

The mean age was 8.3 ± 2.4 years (range 4.4–13.2) at the start of rhGH treatment. The mean height and weight SDS were -2.8 ± 0.8 (median -2.6 , range -5.0 to -1.8) and

Table 1. Baseline clinical characteristics of patients with NS

No.	Sex	Age at start years	Target height cm	Initial height (SDS)	Initial weight (SDS)	Height velocity cm/year	IGF1 (SDS)	IGFBP-3 (SDS)	Heart anomaly	PTPN1 mutation	Mutations in other genes
01	F	10.5	-0.6	-5.0	-3.1	4.5	-1.18	-0.50	Pulmonic stenosis	None	MEK1: p.Y130C
02	F	10.3	-0.8	-1.9	-2.6	4.8	-1.18	-2.13	Atrial septal defect	p.E139D	None
03	M	08.9	-0.8	-3.6	-3.7	4.4	-1.82	-1.44	Pulmonic stenosis	p.N308D	None
04	M	07.8	-NA	-2.7	-3.3	6	-1.69	-0.20	Normal	None	KRAS: p.I36M
05	M	06.8	-0.6	-2.1	-1.7	5.3	-1.07	-0.77	Pulmonic stenosis	None	SOS1: p.E433K
06	M	04.7	-0.3	-2.1	-0.0	5	-1.53	-1.50	Pulmonic stenosis	p.A72G	None
07	M	07.2	-0.3	-1.8	-1.4	4.2	-0.13	-0.50	Patent ductus arteriosus	None	None
08	M	09.9	-0.3	-3.7	-2.7	3.3	-1.96	-1.52	Pulmonic stenosis	p.F285S	None
09	M	07.4	-1.4	-1.8	-1.3	NA	-0.70	-1.33	Atrial septal defect	p.P491S	None
10	M	06.2	-0.4	-2.6	-2.0	6	-0.93	-0.10	Normal	p.Y63C	None
11	M	05.8	-1.4	-2.2	-0.5	6	-0.53	-1.36	Ventricular septal defect	p.P491S	None
12	M	09.2	-0.8	-2.1	-2.1	4.1	-1.74	-0.10	Pulmonic stenosis	None	SOS1: p.R552G
13	M	06.3	-0.8	-3.2	-3.6	6	-0.73	-0.30	Pulmonic stenosis	p.N380S	None
14	M	08.0	-0.5	-2.9	-1.3	NA	-1.86	-0.40	Normal	Not done	Not done
15	F	09.2	-0.2	-2.5	-2.2	NA	-0.95	-0.60	Normal	None	None
16	M	04.4	-0.0	-3.0	-2.8	NA	-0.71	-0.50	Ventricular septal defect	p.N308D	None
17	F	10.2	-0.9	-3.3	-2.7	NA	-0.38	-0.67	Pulmonic stenosis	p.N308D	None
18	M	12.4	-0.5	-3.8	-2.1	NA	-1.98	-1.79	Mitral regurgitation with mitral valve prolapse	None	None

NA = Not available.

-2.2 ± 1.0 (median -2.15 , range -3.7 to 0.0) according to national standards, respectively. The mid-parental height SDS was -0.4 ± 0.7 (range -1.4 to 0.8). Mean bone age was 6.2 ± 2.9 years (median 5.5 , range 2.8 – 11.5 years). All children were prepubertal at the time of enrollment. Of 19 children, 15 had a congenital heart defect such as pulmonic stenosis (9 subjects, 47.4%), secundum atrial septal defect (2 subjects, 10.5%), ventricular septal defect (2 subjects, 10.5%), patent ductus arteriosus (1 subject, 5.3%), or mitral regurgitation with mitral valve prolapse (1 subject, 5.3%).

Response to rhGH Therapy

A 13.2-year-old girl was withdrawn from the study after 6 months of rhGH therapy because she manifested thelarche of Tanner stage II. The growth parameters and clinical characteristics of the 18 children (14 boys and 4 girls) enrolled in the study are shown in table 1. Height SDS increased from -2.8 ± 0.9 at the start of rhGH therapy to -2.0 ± 0.9 after 12 months later ($p < 0.001$). Height velocity increased from 5.0 ± 0.9 cm/year in the year before treatment to 8.9 ± 1.6 during treatment ($p < 0.001$). Serum IGF-1 and IGFBP-3 levels increased

Table 2. Evolution of height SDS, growth velocity, and serum IGF-1 and IGFBP-3 levels during rhGH therapy

	At the start of treatment	After 1 year of treatment	p value
Chronologic age, years	-8.0 ± 2.2	-9.0 ± 2.2	
Bone age, years	-5.9 ± 2.7	-6.0 ± 2.7	<0.011
Height SDS	-2.8 ± 0.9	-2.0 ± 0.9	<0.000
Growth velocity, cm/year	-5.0 ± 0.9	-8.9 ± 1.6	<0.002
IGF-1 SDS	-1.2 ± 0.6	-2.7 ± 2.7	<0.001
IGFBP3 SDS	-1.4 ± 0.5	-0.5 ± 0.8	<0.012

after treatment ($p < 0.001$) (table 2). There were no serious adverse effects during treatment. Spearman rank correlation showed that height SDS after 1 year of rhGH treatment was negatively correlated with the bone age measured at the start of treatment ($r^2 = 0.918$, $p < 0.001$). The other parameters, such as chronologic age at the start of treatment, mid-parental height, and initial serum IGF-1 and IGFBP-3 levels were not statistically significant.

Table 3. Comparison of the rhGH response in patients with NS with and without *PTPN11* mutations

	<i>PTPN 11</i> mutation		p value
	positive (n = 10)	negative (n = 8)	
Chronologic age at start, years	7.4 ± 2.3	8.9 ± 1.9	
Bone age at start, years	5.3 ± 2.6	6.7 ± 2.7	0.154
ΔHeight SDS	0.7 ± 0.4	0.9 ± 0.2	0.288
ΔGrowth velocity	3.6 ± 1.6	3.8 ± 0.8	0.325
ΔIGF-1 SDS	2.0 ± 0.9	4.1 ± 4.1	0.214
ΔIGFBP-3 SDS	0.5 ± 0.3	0.7 ± 0.4	0.182

ΔHeight SDS = height SDS after 1 year of rhGH therapy – height SDS before rhGH therapy; ΔGrowth velocity = growth velocity after 1 year of rhGH therapy – growth velocity before rhGH therapy; ΔIGF-1 SDS = IGF-1 (ng/ml) after 1 year of rhGH therapy – IGF-1 before rhGH therapy; ΔIGFBP-3 SDS = IGFBP-3 (ng/ml) after 1 year of rhGH therapy – IGFBP-3 before rhGH therapy.

Molecular Analyses

Mutations in the *PTPN11* gene were identified in 10 subjects (55.6%). Mutations in the *SOS1* (2 children, 11.1%), *MEK1* (1 child, 5.6%) and *KRAS* (1 child, 5.6%) genes were also found. There were no clinical or laboratory differences between the groups with or without mutations in the *PTPN11* gene. Response to rhGH treatment represented by changes in height SDS, height velocity, and serum IGF-1 level was not significantly different in children with mutations in the *PTPN11*, compared with those seen in children without mutations in *PTPN11* (table 3).

Discussion

This study is a prospective, uncontrolled, observational study of the growth-promoting efficacy of rhGH treatment in children with NS. There was an obvious height gain compared with the national standards. Short stature is a general characteristic of children with NS because of the affected protein of the Ras-MAPK pathway, thus suggesting that deregulation of the Ras-MAPK signaling causes the growth disturbance seen in NS. It has been suggested that there may be a genotype-phenotype correlation with respect to spontaneous growth [16, 17]. The frequently detected upstream defects of this pathway are gain-of-function mutations of *PTPN11*, which are associated with a mild form of GH resistance and IGF-1 defi-

ciency, presumably due to interference with the Janus kinase 2, and the signal transducer and activator of transcription 5b (JAK2-STAT) signaling of the GH receptor. In approximately half of all individuals with NS, the cytoplasmic tyrosine phosphatase SHP2 encoded by *PTPN11* is mutated.

Several studies have reported final height data after rhGH treatment of children with NS [5–9, 18]. However, these studies were relatively small and they lack the matched or randomized controls required for proper comparison. The height gain varied largely in these studies (0.6–2.0 SDS), with the best results reported in those performed in younger age groups at the start of treatment [7, 9]. Interestingly, either the younger the age the rhGH treatment is started [7] or the older age of the start of puberty [9], the better the result. In this study, height SDS after 1 year of rhGH treatment was negatively correlated with bone age at the start of treatment, i.e. the younger the initial bone age, the better the treatment outcome. Subject age at the start of treatment and the duration of rhGH treatment varies widely in the published studies, whereas the mean heights measured at the start of treatment are rather similar. The dosages of rhGH applied in both the case studies and the observational studies tended to be higher than those used in the replacement therapy of GH-deficient patients, although they were lower than those in Turner syndrome patients [19]. Although the different doses of rhGH (33–66 µg/kg/day) were used in previous therapeutic trials, no significant correlation of given dosage to final height has been found in any study [5–7, 9]. In an uncontrolled study of 18 children, the initial dose of rhGH was either 33 or 66 µg/kg/day. Height SDS increased from -2.9 ± 0.4 to -1.2 ± 1.0 after a mean duration of treatment of 7.5 years, however there was no significant difference between doses [7]. It is difficult to compare the effect of rhGH treatment due to variable dose and duration of treatment, different age at start of treatment, small numbers of subjects, and lacking randomization or control groups. Data regarding the benefits of rhGH treatment during childhood and adolescence for increasing the final height, are encouraging in individuals with NS. This study demonstrates that rhGH treatment improved the height SDS, height velocity, and serum IGF-1 level after 1 year in children with NS and without any significant adverse effects. Long-term follow-up should be needed to evaluate the degree of height improvement and IGF-1 increase observed. Although there is no standard data regarding the height and weight of Korean patients with NS, height SDS increased significantly according to Korean normative data. In this study,

the serum levels of IGF-1 and IGFBP-3 were low, and both the serum IGF-1 and IGFBP-3 levels increased significantly. Long-term follow-up will be needed to monitor the efficacy and safety of rhGH treatment.

Studies of postnatal growth provide conflicting data regarding the severity of short stature in mutation-positive and mutation-negative patient groups. NS patients with *PTPN11* mutations were significantly shorter than those without the mutation [20–22]. However, in other studies, there were no differences in the growth parameters between 51 mutation-positive and 64 mutation-negative subjects [23], or in the analysis of growth to the final height in 56 cases [24]. Previous reports independently studied the serum levels of GH-dependent growth factors and the short-term response to rhGH in children with NS related to *PTPN11* mutations as age-related serum IGF-1 levels were found to be lower in children with *PTPN11* mutation [25–27]. However, *PTPN11* mutations were not associated with lower IGF-I levels in the cohort presented here. GH secretion and GH-dependent peptides have been compared in *PTPN11* mutation-positive and mutation-negative subjects [26, 27]. The growth response to rhGH treatment seems to be diminished in subjects who are positive for *PTPN11* mutation [25–27]. This may be due to a mild GH-resistance state in these individuals [25]. In contrast, a recent study demonstrated no difference in the long-term response to rhGH in relation to *PTPN11* mutations [9]. However, it should be noted that 22 of 27 patients in that study had the *PTPN11* mutation, the total number of *PTPN11* mutation negatives treated was low (n = 5). Whether the *PTPN11* mutation or other mutations in the RAS-MAPK pathway are correlated with the growth response to rhGH treatment up to final

height, merits further evaluation in larger prospective and representative studies [28, 29]. Screening for mutations of the *RAF1* and *HRAS* genes before rhGH therapy is important due to the development of progressive ventricular hypertrophy in NS children with *RAF1* mutation [10, 30] and the susceptibility to tumor growth in patients with Costello syndrome [31]. Recently, it has been reported that risk of cancer in patients carrying a mutation in *PTPN11* is higher than the general population, particularly hematological malignancies. However, no clear correlation was found between specific mutations in *PTPN11* and the occurrence of cancer [32]. The strength of the study is that the protocol was designed prospectively and the mutation analysis was performed in most children with comparison between the mutation-positive and -negative groups. Long-term correlation between genotype and rhGH therapy responsiveness needs to be addressed in a large study population because of the short duration of therapy and small number of children in this study.

In conclusion, the rhGH therapy significantly improved growth velocity and increased the serum IGF-1 level. There were no clear differences in the growth parameters at baseline or changes in height SDS and serum IGF-1 levels after rhGH therapy in patients with *PTPN11* mutation and those without *PTPN11* mutation.

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Erratum

It has come to our knowledge that in table 2 of the paper by Choi et al. [Horm Res Paediatr 2012;77:388–393] some errors have occurred. The correct table is as follows:

Table 2. Evolution of height SDS, growth velocity, and serum IGF-1 and IGFBP-3 levels during rhGH therapy

	At the start of treatment	After 1 year of treatment	p value
Chronologic age, years	8.0 ± 2.2	9.0 ± 2.2	
Bone age, years	5.9 ± 2.7	6.0 ± 2.7	0.011
Height SDS	-2.8 ± 0.9	-2.0 ± 0.9	0.000
Growth velocity, cm/year	5.0 ± 0.9	8.9 ± 1.6	0.002
IGF-1 SDS	-1.2 ± 0.6	2.7 ± 2.7	<0.001
IGFBP-3 SDS	-1.4 ± 0.5	-0.5 ± 0.8	0.012