Growth Response, Near-Adult Height, and Patterns of Growth and Puberty in Patients with Noonan Syndrome Treated with Growth Hormone

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Context: Noonan syndrome (NS) is a heterogeneous genetic disorder characterized by short stature.

Setting: The National Cooperative Growth Study (NCGS), a postmarketing observational study of recombinant human GH (rhGH)-treated children, includes a large cohort of children with NS.

Patients: We studied NCGS-enrolled prepubertal and pubertal children with NS.

Main Outcomes: Baseline characteristics and growth responses in NS patients with reported near-adult height (NAH) (n = 65) were compared to patients with idiopathic GH deficiency (n = 3007) and Turner syndrome (TS; n = 1378) with reported NAH to identify factors contributing to NAH optimization in NS.

Results: NS patients (mean enrollment age, 11.6 yr) received rhGH (mean, 0.33 mg/kg · wk) for a mean of 5.6 yr. No significant difference was observed in Δ height SD score (SDS) between NS (+1.4 ± 0.7) and TS (+1.2 ± 0.9). However, Δ height SDS for NS and TS differed significantly from idiopathic GH deficiency (+1.7 ± 1.0) ($P < 0.0001$). Mean gain in NAH above projected was 10.9 ± 4.9 cm (males) and 9.2 ± 4.0 cm (females). Duration of prepubertal rhGH was an important contributor to prepubertal change in height SDS ($r^2 = 0.97$). Height SDS at pubertal onset highly correlated with NAH SDS ($\rho = 0.783$; $P < 0.0001$). Duration of puberty highly correlated with pubertal height gain in centimeters for males ($\rho = 0.941$) and females ($\rho = 0.882$) ($P < 0.01$). No new adverse events were observed.

Conclusions: rhGH significantly improved height SDS for children with NS at NAH. Duration of prepubertal rhGH and height SDS at puberty were important contributors to NAH. Because starting age of the patients in this report was 11.6 yr, these data suggest that greater growth optimization is possible with earlier initiation of therapy. **(*J Clin Endocrinol Metab* 94: 2338–2344, 2009)**

Noonan syndrome (NS) is a clinically heterogeneous genetic condition affecting between 1 in 1000 and 1 in 2500 live births (1). Characterized by Noonan *et al.* (2) in 1963, NS comprises a constellation of features, the most prominent being short stature, congenital heart disease (CHD), early feeding difficulties, and a characteristic facies and body habitus. Short stature is reported in more than 80% of patients affected by NS (1, 3). Birth weight and length are typically normal, but subsequent growth retardation affects height, weight, and bone development, with mean adult height 162.5 cm (63.9 inches) for men and 152.7 cm (60.1 inches) for women (4). Since 1994, when a gene for NS was mapped to chromosome 12 (12q24.1) and a mutation in PTPN11 was identified and characterized in familial cases, at least three other gene mutations have been identified (5–9). While contributing to the broad heterogeneity of NS, these mutations have not completely localized the cause of the short stat-

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Abbreviations: AE, Adverse event; BA, bone age; CA, chronological age; CHD, congenital heart disease; GHD, deficiency; IGHD, idiopathic GHD; NAH, near-adult height; NS, Noonan syndrome; rhGH, recombinant human GH; SAE, serious AE; SDS, SD score; TS, Turner syndrome.

ure or identified the basis of many of the other features of this syndrome. Even if the genetic cohorts are found to have significant height discrepancies, variability in puberty onset/duration could also contribute to differences in height. Thus, a single genetic basis for the short stature is unlikely to be identified at this time. Because near-adult height (NAH) depends, at least in part, on the interplay of GH and sex steroids to stimulate pubertal growth, a better understanding of the typical pattern of puberty in the NS population treated with GH could aid in optimizing adult height.

There is a recent report from a recombinant human GH (rhGH) registry, the KIGS International Growth Database (10), as well as an earlier report (11) and several studies reporting effects of rhGH on NAH in patients with NS (12–14). However, all involved small numbers of patients with varied enrollment ages, treatment durations, rhGH doses, and response.

The National Cooperative Growth Study (NCGS) is a postmarketing observational study established in 1985 with the launch of Genentech's first rhGH product, and it remains the largest North American repository for auxological and clinical outcome data in children with NS and other growth-related disorders. In 1996, using NCGS data, we evaluated the response to rhGH therapy in 150 children with NS compared with those with idiopathic GH deficiency (IGHD) and Turner syndrome (TS) (15). In the present study, we report the NCGS experience with rhGH therapy in a large group of children (n = 370) with NS and a subset analysis of NS enrollees (n = 252) who were naive to GH and on whom we had more than 2 yr of growth data, from which 65 had data to derive NAH. These were compared with NAH data from children with IGHD and TS. For children with NS and reported NAH, increments of height gain for phases of growth (prepubertal and pubertal) were derived, and growth patterns were evaluated to determine which factors contributed to height optimization. We evaluated the mean age at onset, as well as the average duration of puberty, to better elucidate the various pubertal patterns observed in this population. Lastly, we examined safety data to determine whether any new safety concerns were reported.

Subjects and Methods

Subjects

The methods used for NCGS enrollment and data collection have been previously described (16). The diagnosis of NS was established by the treating physician based on the clinical presentation. Mutational analyses were not available for many subjects at the time of enrollment, and the observational design of the NCGS precluded consistent genotypic determination. GH levels were determined at the institution where the child was treated. GH deficiency (GHD) was defined by a peak GH value less than 10 μg/liter in two standard GH provocative stimulation tests.

NAH was defined, recognizing that children may continue to grow after achieving this definition, for patients in whom both chronological age (CA) and bone age (BA) were at least 14 yr for females and 16 yr for males. If BA was not assessed at the last recorded visit, then the time from the last documented BA to the last visit was added to the last BA to derive an estimated BA. Estimated BA was used in 31% of patients, with a mean projection of 1.1 yr added to the last documented BA and a range of up to 3 yr. NAH was also defined for all female and male patients with CA of at least 18 and 20 yr, respectively. In all cases, estimates can only underestimate NAH, and thus the data are conservative. The mean increment in NAH above projected was derived in the same manner as used by Kirk *et al.* (11). Adult height was extrapolated from pretreatment height percentiles on the NS-specific growth chart. This calculation compares baseline height and NAH with Ranke's Noonan-specific standards (4), which represents growth in untreated patients with NS. We adjusted these Noonan-specific standards by the U.S./German normal adult height ratios (male, 176.8/180 cm; female, 163.3/167 cm) to account for mean height differences between American and German populations, and we use this adjusted NS Ranke standard when comparisons are made. Mean increments in NAH for patients with IGHD and TS were derived using Centers for Disease Control (CDC) standards (17) and Lyon TS standards (18), respectively. Because registry data are cumulative and new patients continue to be added, NAH data represent approximately 20–40% of the patients with NS, TS, or IGHD in the database. To characterize pubertal growth patterns (timing and extent) in NS, we used the NS-adjusted average adult height data (mean, -1 SD and -2 SD) plotted against CDC height standards for normal children.

Lastly, the presence of cardiac abnormalities within patients who had NAH data were evaluated to determine whether the existence of concomitant cardiac disease significantly influenced the height outcomes observed.

Safety

NCGS investigators are required to submit nonserious adverse event (AE) or serious AE (SAE) reports to the Genentech Drug Safety Department 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. Investigators are instructed to report all NCGS protocol— defined targeted events, regardless of perceived relationship to rhGH, including malignancy (new or recurrence), diabetes mellitus, slipped capital femoral epiphysis, intracranial hypertension, scoliosis, and pancreatitis.

Statistical methods

U.S. height standards were obtained from CDC 2000 growth reference data (17). Change in height SD score (SDS) was calculated as NAH SDS minus baseline height SDS. BA SDS was calculated as BA minus mean BA for normal subjects of the same age and sex divided by BA SDS for normal subjects of the same age and sex using data from Greulich and Pyle (19).

Differences between groups of patients by etiology were assessed using two-tailed Student's *t* tests. Relationships between variables expressing key growth milestones and height outcome variables were assessed using Pearson correlation coefficients (ρ). Relative predictive value of each variable on height optimization was assessed using stepwise multiple regression models for selected growth outcomes [prepubertal and pubertal height gain and change in (Δ) height SDS] on the subset of patients with complete data (n = 54). A test result was considered to be statistically significant if $P < 0.01$; for the regression analyses, $P < 0.05$ was selected due to the small sample size. Data are reported as mean $\pm$ SD.

Results

Between November 1985 and April 2005, 374 patients with NS were enrolled in the NCGS. Of these, four were excluded from analysis due to the use of high-dose corticosteroids and/or the presence of comorbidities typically not associated with NS (lupus erythematosus, ulcerative colitis, Crohn's disease, and Kartagener's syndrome), leaving 370 patients for analysis. Preexisting

TABLE 1. Baseline and treatment data for patients with NS, IGHD, and TS who have reported NAH compared to total enrolled populations

	NAH			Total		
	NS	**IGHD**	**TS**	**NS**	**IGHD**	**TS**
Baseline						
n	65	3,007	1,378	252	13,655	3,538
Female (%)	46[a]	32	100[b]	31[a]	25	100[b]
Prepubertal (%)	82[c]	65	87[b]	89[b]	79	92[b]
Mean age (yr)	11.6 (3.0)	11.9 (3.1)	11.2 (3.0)[b]	9.8 (3.6)	10.0 (3.9)	9.4 (3.5)[b]
Mean height SDS	−3.5 (1.0)[b]	−2.6 (0.9)	−3.2 (0.9)[b]	−3.3 (1.0)[a,b]	−2.6 (1.0)	−3.0 (0.9)[b]
Mean growth rate (cm/yr)[d]	3.6 (1.6)[c]	4.3 (2.3)	3.9 (2.3)[b]	4.2 (2.3)	4.5 (2.5)	4.3 (2.5)[c]
Mean bone age SDS[d]	−2.7 (1.5)[a]	−2.1 (1.6)	−1.9 (1.6)[c]	−2.8 (1.5)[a,b]	−2.3 (1.5)	−1.8 (1.5)[b]
Mean Tanner target height SDS[d]	−0.3 (0.7)[a]	−0.4 (0.7)	−0.0 (0.7)[b]	−0.3 (0.7)[a]	−0.4 (0.7)	−0.0 (0.7)[b]
Treatment						
GH dose (mg/kg · wk)[e]	0.33 (0.05)[c]	0.31 (0.07)	0.34 (0.06)[b]	0.32 (0.06)[a]	0.32 (0.07)	0.34 (0.06)[b]
Schedule (injections/wk)[e]	6.2 (1.1)	6.1 (1.3)	6.2 (1.2)	6.2 (1.0)	6.2 (1.2)	6.3 (1.1)[c]
Duration of GH (yr)	5.6 (2.6)	5.1 (2.6)	5.3 (2.5)	5.0 (2.6)	4.8 (2.5)	5.1 (2.4)[b]
NAH SDS	−2.1 (1.0)[b]	−0.9 (1.0)	−2.0 (0.9)[b]	NA	NA	NA
Change in height SDS	1.4 (0.7)[b]	1.7 (1.0)	1.2 (0.9)[b]	NA	NA	NA
NAH gain (cm)				NA	NA	NA
Males	(n = 35)	(n = 2,030)				
Noonan standards	10.9 (4.9)	NA	NA			
CDC standards	8.9 (4.8)	12.7 (6.8)				
Females	(n = 30)	(n = 966)	(n = 1,369)			
Noonan standards	9.2 (4.0)	NA	NA			
CDC standards	10.0 (4.2)	11.2 (7.0)	NA			
Lyon standards	NA	NA	9.0 (6.3)			

Data are presented as mean (SD). NA, Not available.

[a] $P < 0.01$ *vs.* TS.

[b] $P < 0.0001$ *vs.* IGHD.

[c] $P < 0.01$ *vs.* IGHD.

[d] Number was smaller due to unreported data.

[e] Average was calculated for each patient, weighted by the number of days at that dose or schedule. Statistics were then calculated from weighted averages.

cardiac disorders were determined from historical data entered into NCGS. Of the 370 patients, 252 (31% female) were naive to rhGH and received treatment for at least 2 yr. Sixty-five (46% female) of these have reported NAH, but with 11 lacking complete descriptive puberty data, rendering them ineligible for the subanalysis of pubertal tempo.

For patients naive to prior rhGH therapy with 2 or more years of rhGH treatment with NS, IGHD, or TS, the baseline characteristics, treatment regimens, and outcomes are summarized in Table 1. Patients with NAH are shown in addition to the overall (total) for each etiology. Because NAH outcomes are derived from the total patient registry, the percentage at NAH is lower than the registry total but not dissimilar from the other groups in Table 1 (NS, 26%; IGHD, 22%; and TS, 39%). Mean age at enrollment for the total population of NS patients (9.8 yr) was similar to the total group of IGHD patients and similar between the NS and IGHD NAH subgroups. Among patients with NAH, those with NS were significantly shorter at baseline than those with IGHD, but they demonstrated a BA deficit similar to those with IGHD. Compared with TS, NS patients were of similar age at enrollment but had greater BA deficits ($P < 0.01$) for both the NAH group (NS, −2.7 ± 1.5; TS, −1.9 ± 1.6) and the total group (NS, −2.8 ± 1.5; TS, −1.8 ± 1.5).

In Table 1, rhGH treatment (dose and duration) and growth data for children with reported NAH were also compared. Mean rhGH doses used in NS were slightly higher than those in IGHD (0.33 ± 0.05 *vs.* 0.31 ± 0.07 mg/kg · wk, respectively) and similar to those used in TS (0.34 ± 0.06 mg/kg · wk). Among patients with NAH, duration of GH treatment was similar for all three etiologies. No statistically significant difference was apparent in the change in standardized height gain (Δ height SDS) between patients with NS (1.4 ± 0.7) and TS (1.2 ± 0.9); however, the Δ height SDS for patients with IGHD was significantly greater (1.7 ± 1.0; $P < 0.0001$) than for both NS and TS patients. For NS, the mean incremental height gain in NAH above projected, using the Noonan standards, was 10.9 cm for males and 9.2 cm for females. Using the CDC standards, Noonan NAH was 8.9 cm for males and 10.0 for females. The IGHD projected height gain using CDC standards was 12.7 cm for males and 11.2 cm for females, and using the Lyon standards, it was 9.0 cm for TS.

In the NS NAH cohort (n = 65), stimulated peak GH levels were available in 50 patients. GH-sufficient patients (56%) were shorter, but not statistically significantly so, at baseline than those with GHD (−3.7 SD *vs.* −3.3 SD). There was no statistically significant difference in Δ height SDS (1.3 *vs.* 1.6; $P = 0.1209$), but NAH SDS (−2.4 *vs.* −1.7) was statistically different between these groups ($P = 0.0134$).

Figure 1 illustrates the improvement in height SDS in rhGH-treated NS males (n = 35) and females (n = 30) who had reported NAH. Females had a larger baseline height deficit than males.

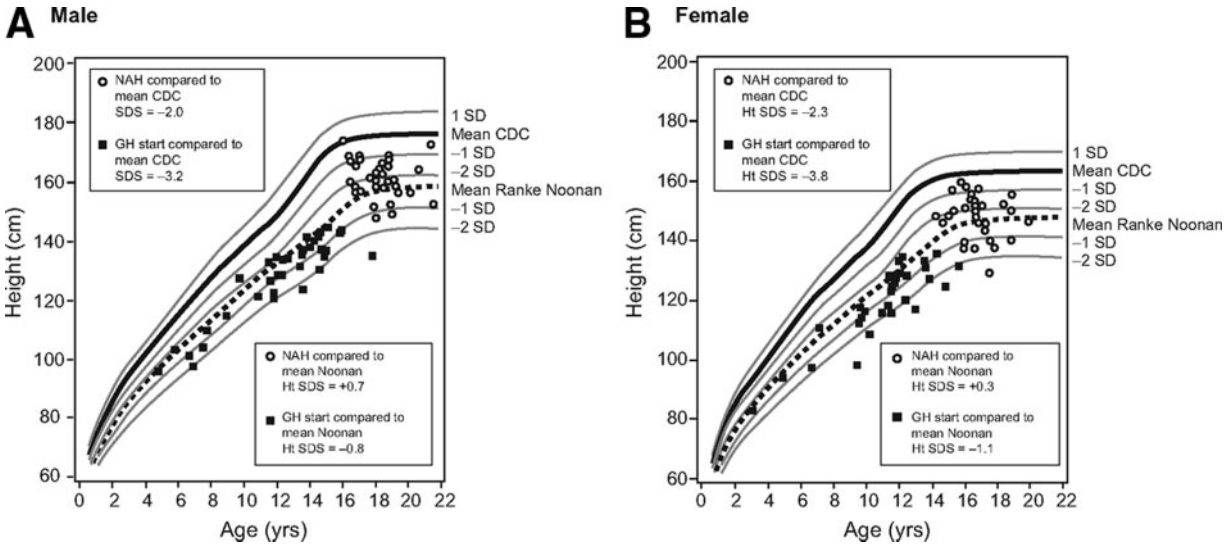

FIG. 1. Height SDS at baseline and at NAH in 35 males (A) and 30 females (B) with NS enrolled in the NCGS, relative to CDC normal (*heavy black line*) and Ranke Noonan (*dashed line*) reference curves.

Males experienced an increase in mean height SDS from −3.2 to −2.0 (CDC standards) and from −0.8 to 0.7 (NS-specific standards), yielding a Δ height SDS of 1.2 (CDC standards) and 1.5 (NS-specific standards) (Fig. 1A). Females experienced an increase in mean height SDS from −3.8 to −2.3 (CDC standards) and from −1.1 to 0.3 (NS-specific standards), yielding a Δ height SDS of 1.5 (CDC standards) and 1.4 (NS-specific standards) (Fig. 1B).

Of the NAH cohort, 30 (46%) had a documented cardiac abnormality. Although data on the severity or need for surgical intervention was not routinely entered in NCGS, there was no statistical difference between the early growth or NAH outcome of the patients with CHD with or without pulmonic stenosis and those without CHD (data not shown).

To assess what factors might be associated with NAH, Pearson correlation coefficients (ρ) were determined for selected variables (Table 2). Duration of prepubertal rhGH treatment was highly correlated with the gain in prepubertal height SDS. Similarly, height SDS at the initiation of puberty was highly correlated with NAH SDS. For all NS patients who reached Tanner stage IV development (25 females, 64 males), the duration of puberty from Tanner stage II to IV had a strong positive correlation with pubertal height gain in centimeters. However, because data for all pubertal stages were insufficiently reported for those patients who reached NAH, we couldn't correlate duration of puberty with NAH. Age of pubertal onset was inversely correlated with pubertal height gain in centimeters in both males and females. These findings suggest that those with an earlier onset of puberty had a longer pubertal growth period contributing to a greater height gain during puberty.

TABLE 2. Evaluating the relationship between variables to assess the impact on height, height gain, and NAH

Variable	Variable	n	PCC (ρ)	*P*
Years of prepubertal GH	Prepubertal Δ height SDS	54	0.722	<0.0001
Height SDS at start of puberty	NAH SDS	54	0.783	<0.0001
Pubertal duration				
Males	Height gain in cm, Tanner stages II–IV	64	0.941	<0.0001
Females	Height gain in cm, Tanner stages II–IV	25	0.882	<0.0001
Age of pubertal onset				
Males	Height gain in cm, Tanner stages II–IV	64	−0.499	<0.0001
Females	Height gain in cm, Tanner stages II–IV	25	−0.628	0.0008

PCC, Pearson correlation coefficient.

The relative importance of other selected baseline and treatment characteristics on height outcome measures was investigated using multiple regression analyses (data not shown). Duration of treatment accounted for the largest proportion of the variance in height gain in centimeters during both prepubertal (97%) and pubertal (73%) years. Duration of rhGH also accounted for 52 and 11% of the variance, respectively, of the Δ height SDS from baseline to pubertal onset and from pubertal onset to NAH. Height SDS at enrollment accounted for 64% of the variance in height SDS at the start of puberty and 61% of the variance in NAH SDS. Results of additional analyses during puberty in NS patients showed that the change in height SDS was significant during this period. For patients with sufficient puberty data for assessment, regardless of NAH, the mean change in height SDS (SD) was 0.45 (0.59) (95% confidence interval, 0.32–0.57; $P < 0.0001$) for a test of whether this change was zero. Similar results for those with NAH showed a mean change in height SDS (SD) of 0.51 (0.56) (95% confidence interval, 0.33–0.69; $P < 0.0001$) for a test of whether this change was zero.

In a separate analysis of first-year growth response, there was no significant effect of height SDS at enrollment on first-year velocity (centimeters per year) in NS ($P = 0.4691$), whereas a marginal effect was seen in TS ($P = 0.0597$) and a significant inverse effect was seen in IGHD ($P < 0.0001$). Analyses for patients with NS and IGHD were controlled for enrollment age,

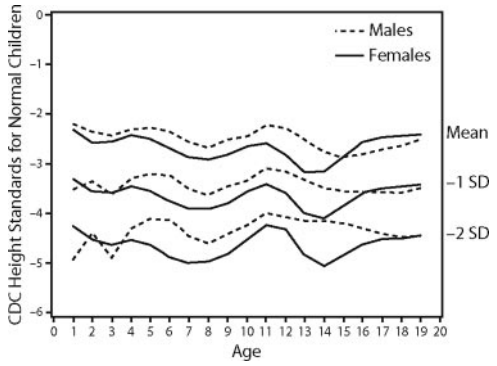

FIG. 2. Mean, −1, and −2 height SDS curves by age for non-rhGH treated males (*dotted lines*) and females (*solid lines*) with NS. These curves were derived using NS-specific standards and plotted on a CDC chart to allow comparison with normal children. The NS-specific standards were also adjusted for U.S./German normal adult height ratios (male, 176.85/180; female, 163.34/167) to account for mean height differences between the American and German populations. The *left vertical axis* is calibrated from 0 to −6 SD for CDC height standards that can then be related to adjusted Noonan-specific standards (mean, −1 SD, −2 SD) on the *right vertical axis*.

sex, and dose; analyses for patients with TS were controlled for enrollment age and dose.

We further evaluated the timing and duration of puberty in the NAH population. The mean age of pubertal onset in NS was delayed compared with the overall U.S. population (20–22), but this delay was not uniform. The mean age at Tanner stage II development was 13.4 yr (range, 10.8–16.4 yr) in males, with 35% entering puberty later than age 13.5 yr, and 13.0 yr (range, 10.9–15.0 yr) in females, with 44% entering puberty later than age 13 yr. The age at the onset of Tanner stage IV development for males was 15.7 yr (range, 11.3–19.4 yr) and for females, 15.4 yr (range, 13.4–18.4 yr). The progression from Tanner stage II to IV development occurred in less than 2 yr in 52% of males and 38% of females.

Figure 2 illustrates age-specific, mean height SDS for untreated male and female NS patients derived from the Ranke standards. These standards were adjusted for average adult height by using the ratio of U.S. to German mean adult height. The U.S.-specific mean height standard for untreated NS children was also computed by CDC standards to provide context. Lastly, height standards for −1 and −2 SD values were calculated and graphed. Thus, Fig. 2 depicts a comparison of average untreated NS children to the CDC standards for U.S. children, with the U.S. means on the y-axis to the left and the Noonan means on the y-axis to the right. These untreated NS patients demonstrate a significant height deficit when compared with their CDC-standard peers. Additional relative height was lost after 11 yr of age, when average children begin puberty. Females who attained a higher prepubertal SDS (mean or −1 SD) regained this relative height loss during subsequent pubertal development. In contrast, none of the males or the shortest females (−2 SD) regained the relative height loss occurring during puberty.

Safety

In the total group of 370 NS patients identified in the NCGS, 43 AEs were reported in 33 patients. Twelve were serious, and 31 were nonserious. We further classified them as related to known comorbidities in NS. In addition, we looked at all other SAEs and nonserious AEs. Increased biventricular hypertrophy (n = 1) and hypertrophic cardiomyopathy (n = 1) were considered to be comorbidities of NS. Other AEs associated with known comorbidities of NS included lymphedema, supravalvular aortic stenosis, development of a mandibular and recurrence of a previously diagnosed maxillary giant cell granuloma in the same patient, cryptorchidism, and attention deficit hyperactivity disorder (n = 1 for each). There were six cases of scoliosis. SAEs that were not associated with NS comorbidities included idiopathic thrombocytopenic purpura, Crohn's disease, bronchitis, brain neoplasm (possible left parietal lobe tumor of unknown type), nephrotic syndrome, and respiratory distress (associated with a viral infection). Nonserious AEs included injection site reactions (n = 3), rash (n = 3), edema (n = 2), gynecomastia (n = 2), wrist fractures (n = 2), and osteochondrosis (n = 1).

Discussion

In 1996, we reported that 4 yr of rhGH therapy was associated with a significant increase in growth rate over baseline in 150 previously untreated children with NS (15). The mean growth rate in children with NS was intermediate between those with IGHD and TS but differed significantly from both. Other experience with rhGH treatment in NS patients has demonstrated positive effects on growth without significant AEs (11, 23). However, adult height outcomes of children with NS treated with rhGH have only recently been elucidated (10–14).

In the present report, treatment with rhGH significantly improved height SDS for NCGS-enrolled children with NS who have reported NAH; this increase is similar to the change seen in TS patients, although significantly less than in IGHD. However, because there is greater heterogeneity in the heights of untreated NS patients, with more in the normal range than untreated TS patients, the NS patients in this study may represent a shorter subset than those of TS. Based on the NS reference standards and the approach suggested by Kirk *et al.* (11), the mean incremental height gain in NAH with rhGH treatment was 10.9 cm for males and 9.2 cm for females. As in other populations of rhGH-treated patients, NS females are shorter than males at start of therapy (−3.8 *vs.* −3.2 SD). This is likely due to ascertainment bias and delayed referral of females and has been well-described in rhGH registries (15). It should also be noted that because these data are from a registry and not a clinical trial where all patients are followed until treatment is complete, these height data may underrepresent the final height that will be achieved by those patients who have started rhGH at a young age and are still being treated at the time of this analysis.

AEs known to be associated with rhGH, and prespecified in the protocol as reportable events, were not unduly represented in the NS population. There were no cases of slipped capital femoral epiphyses, intracranial hypertension, pancreatitis, or diabetes. The most commonly reported event was the associated event, scoliosis (n = 6), which also appears to be a comorbidity of NS (24, 25). Three cardiac events were reported as AEs during the course of rhGH therapy (increased biventricular hypertro-

phy, hypertrophic cardiomyopathy, and supravalvular aortic stenosis). There were isolated reports of other comorbidities typically associated with NS. The remaining SAEs and nonserious AEs did not follow any particular pattern.

Comparisons between this study and the most recent NS study from the KIGS database (10) are difficult because median values were reported in the latter cohort of 24 patients at or near final height. However, both achieved significant increases in NAH. The earlier UK-KIGS study by Kirk *et al.* (11) demonstrating only 3.1 cm incremental NAH height gain may be explained by the small number (n = 10) of patients at NAH and the fact that in the entire cohort, 78% had cardiac malformations and 48% had corrective cardiac surgery, whereas cardiac disorders were less frequent (46%) in our cohort and of a severity that did not affect final height compared with those unaffected. Our NAH outcomes were not quite as good as those reported by Osio *et al.* (12) involving 18 NS patients (13.0 cm for males and 9.8 cm for females); however, their cohort was younger at enrollment (8.6 *vs.* 12.1 yr in males and 7.7 *vs.* 11.0 in females), was treated longer (7.5 *vs.* 5.6 yr), and did not include patients with significant heart disease. The variable results shown by Municchi *et al.* (13) (Δ height SDS of 1.8, 1.0, 0.3, and −1.2 in four enrollees) may be due to the lower average doses (0.19–0.31 mg/kg · wk), older enrollment age (13.5 yr), or shorter treatment duration (3.5 yr). Finally, our data corroborate the findings in the recently reported Noordam cohort (14), in which 29 patients were similar in enrollment age (11 yr), treatment duration (median, 6.4 yr), rhGH dose (0.35 mg/kg · wk), and gain in height SDS (mean, 1.3 SD per national and Noonan standards). In addition, they were genetically characterized for PTPN11 mutations (22 of 27), but no differences in the long-term responses between those with or without the mutation were found, which suggests that their results and ours are likely clinically relevant to those with or without the PTPN11 mutation.

Taken together, these studies demonstrate that earlier initiation and longer duration of rhGH therapy are associated with improved NAH outcomes. Our evaluation of factors contributing to height optimization in NCGS patients with NS supports this observation. In NS, similar to the responses observed in other growth-related disorders (26–28), we found that a longer duration of rhGH therapy during the prepubertal period resulted in a greater gain in prepubertal height SDS. That the NS patients had a greater prepubertal delay in BA than those with TS suggests that in some patients there may be a component of constitutional growth delay, which may allow for a longer period of growth in the prepubertal period. However, even the otherwise normal child who has a constitutional growth pattern may not catch up completely to expected midparental height (29). It is unlikely for the patient with NS to grow sufficiently in puberty to compensate for the height deficit present at puberty start. We also show that the duration of puberty, which corresponds to the length of time rhGH can continue to affect growth, also correlated with greater pubertal height gain. These findings are similar to those recently reported in patients with TS in whom final height was affected by age at GH initiation, height SDS at pubertal onset, and duration of GH therapy (30). Age at pubertal onset was inversely related to the pubertal height gain in centimeters in both males and females. An earlier onset may allow for a longer puberty and consequent pubertal rhGH treatment duration. These findings are consistent with those described by Ranke's mathematical model for total pubertal growth, demonstrating that an earlier pubertal onset is associated with increased total pubertal growth (31). We also looked at the issue of whether those who start puberty late go through puberty at a faster pace and confirmed that they did, with the duration of puberty accounting for approximately 20% of the variance in height gain during puberty.

Assessing growth outcomes in puberty is complex, and even more so for patients with NS who typically have pubertal delay. As illustrated in Fig. 2, untreated NS patients lose additional relative height when their normal peers start puberty (at approximately 11 yr of age), and this loss in height is generally not regained during the pubertal growth spurt. The lack of sufficient pubertal catch-up growth is a consistent finding in males, resulting in the loss of another −0.3 to −0.4 SD during puberty in addition to their previous deficit. Although females regain more height, ranging from −0.2 to +0.2 SD during puberty, they remain significantly short compared with normal girls. For both males and females, the amount of catch-up growth is directly related to the height SDS at pubertal onset. This finding argues against the concept that the growth pattern in some with NS represents a constitutional delay with appropriate catch-up growth. Furthermore, this lack of catch-up growth could be further exacerbated when accompanied by a normal to fast (< 2 yr), rather than prolonged, progression through puberty as we observed in 52% of males. These growth patterns in NS underscore the importance of normalizing and optimizing height by the onset of puberty. The curves in Fig. 2 also illustrate the difficulty with expressing height gain by Δ height SDS for an index population with such variability in puberty when compared with the normal population for whom the SDS values were established. This clinically challenging issue was recently described by Bakker *et al.* in patients with GHD, idiopathic short stature, and TS (32). In the present study, we report both height gain in centimeters and Δ height SDS as treatment endpoints. However, an important caveat to our findings is that only NAH data, not final height, were available for our analyses.

Analysis of the height gain by looking at those NS patients that were classified as GH sufficient *vs.* those classified as GHD failed to show a significant difference in their Δ height gain. That their final heights were statistically different (the sufficient shorter than the deficient) is likely a function of the trend to the sufficient being somewhat shorter at start. That first-year growth in NS, as an indicator of rhGH responsiveness, did not correlate with height SDS at start, and differed from that in IGHD, in which the correlation was inverse, supports the analysis that provocative test results for GH were not a differentiating factor in rhGH responsiveness in this series of NS patients.

In conclusion, rhGH therapy significantly improved height SDS for NCGS-enrolled children with NS (+1.4) who reached NAH; this gain was statistically similar to that seen in TS (+1.2), although significantly less than in IGHD (+1.7). The presence or absence of CHD or pulmonic stenosis did not appear to affect growth outcomes in this population. Puberty in children with NS

is typically delayed, and prepubertal growth plays an important part in attainment of NAH, although a prolonged and delayed puberty is not a uniform finding. Therefore, if the clinician generalizes this finding to all patients with NS, and accordingly, withholds or delays GH treatment, severe short stature may result because of inadequate pubertal catch-up growth. The relatively common occurrence of rapid pubertal progression may further compromise potential stature. Earlier initiation of rhGH therapy and longer prepubertal duration of therapy result both in improved height SDS at pubertal onset and in a more salutary NAH.

Acknowledgments

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