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Growth hormone treatment in Noonan syndrome: The National Cooperative Growth Study experience

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We evaluated the response to growth hormone (GH) therapy in 150 children (97 boys) with Noonan syndrome (NS) by analyzing growth data from children with NS who were enrolled in the National Cooperative Growth Study and compared those data with National Cooperative Growth Study growth data from children with idiopathic growth hormone deficiency (IGHD) and Turner syndrome (TS). Children with NS were significantly shorter than those with IGHD and TS. The annualized growth rates for years 1, 2, 3, and 4 of therapy in patients with NS who were naive to previous GH therapy were significantly greater than baseline. Their growth rates for years 1, 2, 3, and 4 were intermediate between those in children with IGHD and TS and were significantly different from both. A significant improvement occurred in height SD scores for those 42 children with NS who have been monitored for at least 4 years of GH therapy. Three of six boys with NS for whom adult height data were available exceeded their pretreatment predicted heights. (J Pediatr 1996;128:S18-21)

Noonan syndrome is a well-established entity with an estimated incidence of 1 in 2500 to 1 in 1000.[1] Characterized by Noonan et al.,[2,3] NS comprises a constellation of physical features, the most prominent of which are short stature, congenital heart disease, and a characteristic facies and body habitus. This syndrome has been known by various names (e. g., male Turner syndrome, pseudo-Turner syndrome, Ullrich-Turner phenotype). In the absence of a specific diagnostic marker, NS remains a clinical diagnosis.

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Short stature occurs in more than 80% of patients.[4,5] Patients typically are of normal birth weight and length but subsequently have growth retardation involving height, weight, and bone development. Their heights and weights are usually below the third centile, and mean final adult heights are 162.5 cm for men and 151 cm for women.[6] No consistent abnormality in the secretory dynamics of growth hormone has been reported in these children. Experience

BA	Bone age
GH	Growth hormone
GR	Growth rate
HA	Height age
IGHD	Idiopathic growth hormone deficiency
NCGS	National Cooperative Growth Study
NS	Noonan syndrome
SDS	Standard deviation score(s)
TS	Turner syndrome

with GH therapy in NS has been limited to small studies of short duration.[7-13] Growth rates have increased during GH therapy without reports of adverse reactions. The National Cooperative Growth Study, the postmarketing observation study[14] that accompanied the introduction of biosynthetic methionyl-GH (somatrem, Protropin; Genentech, Inc., South San Francisco, Calif.), has provided a large database that includes data from 150 patients with NS. These data make it possible to analyze the growth response to GH in children with NS and to compare that response with the response in children in the NCGS with idiopathic growth hormone deficiency and TS.

MATERIAL AND METHODS

Subjects. The methods of subject enrollment and data collection have been previously described.[14] The NCGS includes 150 prepubertal and pubertal children (97 boys) with NS who had not been treated with GH before enrollment (data collection: June 1986 through February 1995). The diagnosis of NS was made by the treating physician. The enrollment forms included reports of congenital heart disease in 42% of these children and dysmorphic features in 76% of them. Relevant concomitant medications were levothyroxine ($n = 16$), sex steroids ($n = 23$), glucocorticoids ($n = 2$), desmopressin ($n = 1$), luteinizing hormone-releasing hormone analogs ($n = 2$), methylphenidate hydrochloride ($n = 7$), and β-blockers, diuretics, or both ($n = 4$). The GH levels were determined at the institution where the child was treated.

Statistics. The data are reported as the mean ± SD. Height SD scores for age and sex were calculated as follows: SDS = (height – mean height for normal subjects of the same age and sex)/(SD of height for normal subjects of the same age and sex). Height and weight standards were obtained from data collected by the National Center for Health Statistics.[15] Height standards for children with NS were obtained from data collected by Ranke et al.[6] The bone age SDS was calculated in a similar manner with data from Gruelich and Pyle.[16] The (Δ HA – Δ BA) and (Δ BA/Δ HA) were calculated as follows: For each patient in each group the time between the first and the last BA was determined, and the change in HA and BA was calculated. The mean difference between and the ratio of the Δ HA and the Δ BA were then calculated for each group.

RESULTS

The mean height SDS at enrollment was –3.5 standardized to normal growth data from the National Center for Health Statistics[15] and –1.35 standardized to the NS growth data of Ranke et al.[6] The stimulated peak GH levels were less than 10 μg/L in 45% of the children, but their response to GH therapy was no different from that in children with stimulated peak GH levels greater than 10 μg/L.

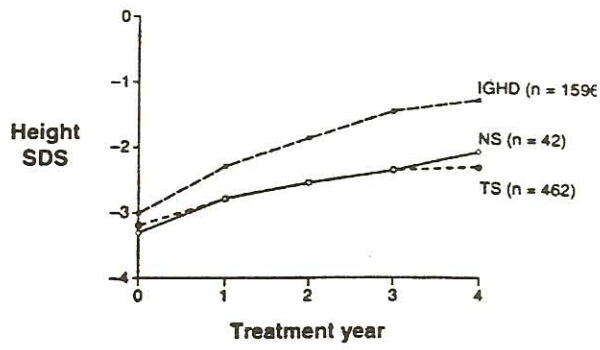

Figure. Height SDS in patients with IGHD, TS, and NS in NCGS

Baseline characteristics of patients with NS, IGHD, and TS are shown in Table I. The ages at enrollment were similar for all groups, but patients with NS were significantly older than those with IGHD ($p = 0.012$). Children with NS were significantly shorter (height SDS, -3.5 ± 1.1; $p \leq 0.001$) and had a significantly greater BA deficit (IGHD: $p < 0.05$; TS: $p = 0.0001$). Their parental heights and weight-for-height SDS were similar to those of children with IGHD. Patients with NS and TS had the shortest Bayley-Pinneau–predicted adult heights.

Treatment growth data for children with NS, IGHD, and TS are shown in Table II. Patients participated in the NCGS for a mean of 3 years. The Δ HAs were similar for children with NS and IGHD. The average GH doses in children with NS and TS were higher than those in children with IGHD, but the differences were not clinically relevant. The baseline growth rates were similar in all groups. The GRs for years 1, 2, 3, and 4 of therapy in patients with NS were significantly greater than baseline ($p \leq 0.003$). The GRs were greatest in children with IGHD, followed by those with NS and then TS. The height SDS by year of treatment are shown in the Figure. The height SDS in the 42 children with NS who have been monitored for at least 4 years of GH therapy progressively improved from -3.3 ± 0.9 to -2.8 ± 1.1, -2.6 ± 1.1, -2.4 ± 1.1, and -2.1 ± 1.2 after 1, 2, 3, and 4 years of therapy, respectively.

Six patients (all boys) reached heights considered to be their final heights (BA ≥17 years). The mean duration of treatment was 4.6 ± 0.7 years, and the mean age at enrollment was 13.6 ± 1.2 years. The secretory dynamics of GH were mixed. Three of these patients reached heights greater than their Bayley-Pinneau–predicted heights.

The relation between the Δ HAs and the Δ BAs for children with NS, IGHD, and TS are shown in Table III. The negative difference between the Δ HA and the Δ BA was greatest in patients with NS. The Δ BA/Δ HA ratio was the same in patients in NS and TS (1.1), and this ratio was higher than that in patients with IGHD.

Table I. NCGS baseline data

	Noonan syndrome	Idiopathic GH deficiency	Turner syndrome
No. of patients	150	8091	2094
Boys	97	5892	0
Girls	53	2196	2094
Age (yr)	10.6 (3.8)	9.8 (4.4)	10.4 (3.5)
Height age (yr)	6.8 (2.9)	7.1 (3.7)	6.9 (2.5)
Height SDS	−3.5 (1.1)	−2.8 (1.1)	−3.2 (0.9)
Bone age SDS	−2.9 (1.7)	−2.5 (1.6)	−2.1 (1.8)
Maternal height SDS	−0.8 (1.6)	−0.7 (1.2)	−0.3 (1.2)
Paternal height SDS	−0.4 (1.1)	−0.4 (1.3)	−0.1 (1.2)
Weight-for-height SDS	0.2 (1.2)	0.2 (1.5)	1.2 (1.5)
Bayley-Pinneau predicted height SDS	−2.3 (1.3)	−1.6 (1.3)	−3.0 (1.1)
Tanner target height SDS	−0.4 (0.8)	−0.4 (0.8)	−0.1 (0.8)

Values are mean (SD).

Table II. NCGS growth data

	Noonan syndrome	Idiopathic GH deficiency	Turner syndrome
Time in NCGS (yr)	3.0 (1.8)	2.7 (1.9)	2.8 (1.7)
Δ Height age (yr)	3.2 (1.9)	3.3 (2.3)	2.6 (1.6)
Average GH dose (mg/kg per wk)	0.31 (0.06)	0.29 (0.06)	0.33 (0.06)
Growth rate (cm/yr)			
Baseline	4.3 (2.3)	4.5 (2.8)	3.9 (2.3)
Year 1	8.0 (2.0)	9.8 (3.0)	7.4 (2.0)
Year 2	6.9 (1.7)	8.1 (2.1)	6.0 (1.7)
Year 3	6.3 (1.5)	7.2 (2.1)	5.2 (1.7)
Year 4	5.7 (1.9)	6.7 (2.1)	4.8 (1.7)

Values are mean (SD).

Table III. NCGS Δ height age and Δ bone age

	Noonan syndrome			Idiopathic GH deficiency	Turner syndrome
	All (n = 86)	BA SDS <−3 (n = 40)	BA SDS >−3 (n = 46)	(n = 3728)	(n = 1113)
First to last BA (yr)	3.3 (1.6)	3.4 (1.5)	3.2 (1.7)	3.1 (1.6)	2.9 (1.4)
Δ HA (yr)	3.4 (1.6)	3.4 (1.5)	3.4 (1.8)	3.6 (2.0)	2.6 (1.4)
Δ BA (yr)	3.8 (2.0)	4.1 (2.2)	3.5 (1.9)	3.6 (2.3)	2.8 (1.9)
Δ HA − Δ BA (yr)	−0.4 (1.1)	−0.7 (1.2)	−0.1 (0.9)	0.0 (1.3)	−0.2 (1.1)
Δ BA/Δ HA	1.1 (0.5)	1.2 (0.5)	1.0 (0.5)	1.0 (0.6)	1.1 (0.7)

Values are mean (SD).

To elucidate a possible relation between the degree of BA delay and the Δ BA with the Δ HA, we calculated the Δ BA/Δ HA ratio in those with BA SDS less than −3 (most delayed) and those with BA SDS greater than −3 (least delayed) for each group. Data for patients with NS are shown in Table III. The Δ BA/Δ HA ratio was greatest in those with the greatest delay in BA at enrollment (BA SDS <−3) and least in those with the least delay in BA at enrollment (delta BA SDS >−3). The Δ BA/Δ HA ratio in children with NS who had a BA SDS greater than −3 was the same as that in children with IGHD (1.0).

A small number of adverse experiences have occurred in children with NS during GH therapy. These include joint swelling in the hand and knee (n = 1), transient hand and facial edema (n = 1), a raspy voice (n = 1), and recurrence of a previously diagnosed maxillary giant cell tumor that was considered remotely related to GH therapy (n = 1).

DISCUSSION

The patients with NS in the NCGS were short even by NS standards, because their height SDS was −1.35 according to the NS growth curves. As a group they were older and shorter and had a greater BA deficit than children in the NCGS with IGHD. Forty-two percent of these patients were reported to have congenital heart disease. In light of the known prevalence of cardiac lesions in NS, this occurrence represents a selection bias or was underreported. Among all the patients with NS in the NCGS, no significant adverse experiences were reported during GH therapy. This is reassuring and is consistent with the published accounts of GH use in NS, including those that have investigated potential cardiovascular effects.[11, 13]

Treatment with GH resulted in sustained growth for 4 years. It is not surprising that the GRs in children with IGHD were greater than those in children with NS. However, the GRs in children with NS exceeded those in girls with TS.

Three of the six patients who achieved their final heights (those with a BA ≥17 years) achieved a height greater than their Bayley-Pinneau predicted height. These results are promising, especially in light of their relatively older age at enrollment (13.6 ± 1.2 years).

To assess the sustained 4-year growth in the face of limited final height data, we examined the relative changes in BA and HA. Initial analysis of the growth data showed that children with IGHD have a Δ BA/Δ HA ratio of ~1 (1.02) and those with NS have a Δ BA/Δ HA ratio greater than 1 (1.12). This finding suggests that the BA in children with NS might advance disproportionately relative to the gain in HA. However, when the delay in BA was considered (separating each group into those with BA SDS <−3 and those with BA SDS >−3), these differences were negligible between groups. Hence the apparent initial advance in BA relative to HA is not unique to NS and may reflect the greater BA deficit in these patients at enrollment. Growth hormone seems to normalize the BA, and because these patients with NS had a more delayed BA, it appears to advance faster.

We conclude that GH therapy results in sustained growth for 4 years in children with NS. Patients with NS have greater GRs than girls with TS for years 1, 2, 3, and 4 of GH therapy. It is promising that some patients have exceeded their predicted heights. The apparent initial advance in BA relative to HA is not unique to NS and may reflect a greater baseline BA deficit. Hence early diagnosis and initiation of GH therapy would be expected to optimize outcome. Grow hormone therapy seems to be safe in children with NS, b cause no significant adverse experiences have been report during treatment.

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