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Growth Hormone Treatment in Noonan Syndrome: Report of Four Cases Who Reached Final Height

G. Municchi[a]
A.M. Pasquino[a]
I. Pucarelli[a]
S. Cianfarani[b]
F. Passeri[a]

Pediatric Endocrinology Unit,
Pediatric Department,
[a] University 'La Sapienza' and
[b] II University, Rome, Italy

Key Words
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Abstract
Final height of 4 patients with Noonan syndrome and short stature treated with growth hormone (GH) is reported. Four prepubertal girls (chronological age 12.3–15.1 years, bone age 11.0–11.5 years) were treated with recombinant human growth hormone (0.5 IU/kg/week s.c.) for at least 3 years. Stimulated GH secretion was normal, spontaneous nocturnal GH secretion was low in 1 patient. Final height, as standard deviation score according to Ranke-specific standards for Noonan syndrome, improved in 3 patients and 2 of them exceeded their corrected midparental height.

Short stature is present in about 80% of patients with Noonan syndrome, characterized by a Turner-like phenotype with no chromosomal abnormality [1]. Intrauterine growth is normal, but during infancy and childhood deceleration of statural growth takes place; pubertal growth spurt is delayed and, according to the data in the literature, mean final height is about 2 SD below the mean of the normal population [2, 3]. The pathogenesis of growth retardation is unknown and evaluation of somatotropic function, performed in a few patients, led to contradictory results [4–6]. Minimal information is available on growth hormone (GH) treatment [5–7]; to our knowledge, no data on final height of GH-treated Noonan patients have been reported.

We report our results of long-term GH treatment on final height in 4 patients with Noonan syndrome.

Patients and Methods

Four prepubertal girls with Noonan syndrome were studied. Diagnosis was made on the basis of facial dysmorphic features, ocular and cardiac abnormalities; mental retardation was present only in 1 patient; karyotype was normal [8]. One patient had atrial septal defect and 3 patients had pulmonary stenosis which did not require surgical correction. The mothers of patients 1 and 3 had short stature (147 and 144 cm, respectively) but did not show any other sign suggestive of Noonan syndrome.

Chronological age ranged from 12.3 to 15.1 years and bone age ranged from 11.0 to 11.5 years. All patients had a height < 3rd centile according to Tanner standards and within the normal range according to Noonan standards reported by Ranke et al. [3]. The pretreatment clinical data of the patients are presented in table 1. GH standard provocative tests (clonidine, arginine and insulin) were performed during the pretreatment observation period. Spontaneous nocturnal GH secretion (sampling every 30 min from 20:00 to 08:00 h) was also studied. The peak GH response to provocative stimuli was normal in all patients (>10 μg/l), whereas spontaneous nocturnal GH secretion was below 3 μg/l in 1 patient (No. 3). The girls were treated with recombinant human growth hormone (rhGH) at a dose of 0.5 IU/kg/week divided into six weekly doses given sub-

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A.M. Pasquino
Pediatric Endocrinology Unit
Pediatric Department, University 'La Sapienza'
Viale Regina Elena 324
I-00161 Rome (Italy)

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Table 1. Clinical characteristics and auxological data during and after GH treatment in 4 girls with Noonan syndrome

Patient No.	CA years	BA years	GV (cm/years) on RX				Height (SDSR) on Rx				Final height		Midparental height, cm
			0	1 y	2 y	3 y	0	1 y	2 y	3 y	SDSR	cm	
1	13.2	11.0	4.3	9.0	5.5	4.7	−0.7	+1.0	+0.6	+0.9	+1.1	156.0	149.5
2	15.1	11.0	3.3	3.5	3.2	2.0	−1.9	−1.4	−1.1	−0.9	−0.9	145.0	159.0
3	13.3	11.0	4.5	7.6	5.3	1.9	+0.1	+0.4	+0.3	+0.4	+0.4	151.8	145.0
4	12.3	11.5	4.6	6.0	2.2	1.3	+0.2	+0.4	+0.1	−0.5	−1.0	143.8	158.5

CA = Chronological age; BA = bone age; GV = growth velocity; SDSR = standard deviation score according to Ranke-specific standards for Noonan syndrome.

cutaneously in the evening; the dose was increased to 0.8 IU/kg/week after 1 year of treatment, according to the study protocol used at that time in our patients with Turner's syndrome. Patients received GH for a period longer than 3 years (3 girls for 3 years and 6 months, and 1 for almost 4 years). Bone age was determined according to the method of Greulich and Pyle [9]; height was expressed in standard deviation score for chronological age for Noonan syndrome standards according to Ranke (SDSR) [3]. Growth velocity expressed in centimeters/year was determined from the height increment during a 6- to 12-month period. Plasma GH was measured in duplicate by polyclonal radioimmunoassay using a commercial kit (Ares-Serono Diagnostic, Milan, Italy). The sensitivity of the assay was <0.2 µg/l.

Results

After the first year of treatment, growth velocity markedly improved compared to pretreatment values in 3 patients and did not significantly change in 1 patient (No. 2). Subsequently, in the responders a 'waning effect' was observed (table 1). After 3 years of therapy, patient 1 discontinued treatment for noncomplicance, the other 3 patients discontinued during year 4 because growth velocity decreased to <1 cm/year. Patients were evaluated until the attainment of final height and all of them, except for patient 4, showed an improvement of height in SDSR which was more evident in patients 1 and 3 who exceeded their corrected midparental height (149.5 and 145 cm, respectively) (table 1). After 4–5 months of GH treatment the girls showed pubertal progression and menarche occurred in 3 patients (cases 1, 3 and 4) after 2 years and in 1 patient (No. 2) after 2.5 years of GH treatment. The interval between B2 Tanner stage and menarche was about 18 months in the first 3 patients and about 24 months in the other patient (fig. 1). During treatment no variation of different metabolic parameters (routine clinical chemistries, oral glucose tolerance test, thyroid function) or cardiac function (assessed both clinically and by echocardiography) was observed.

Discussion

There are only three studies describing GH treatment in patients with Noonan syndrome and two of them are short-term reports: one describing 3 children treated with 0.1 IU/kg 3 times/week for 6–9 months did not find any improvement in growth velocity [5]; the other study, on the contrary, demonstrated a significant improvement in growth velocity in 5 patients after 1 year of GH therapy at a dose of 0.1 IU/kg/day s.c. 6 days/week [6]. The patients reported in a long-term study were treated for a mean of 2.9 years (range 1.8–4.6) and showed improvement in height velocity SDS and subsequently in height SDS [7]. In our small group of patients, treatment with GH showed variable results: final height in SDSR improved in 3 patients and 2 of them exceeded their corrected midparental height. Since only 1 of the 3 patients who responded to GH treatment showed insufficient nocturnal GH secretion, we cannot hypothesize that the GH secretory status has a predictive role in the GH treatment response in Noonan syndrome. Our patients were treated during a peripubertal age and showed sexual development with a growth spurt higher than that reported in untreated subjects [2, 3]. Final height, even though the duration of puberty was shortened probably by treatment, at least in comparison with untreated patients, improved in 3 subjects. The relative older age of our patients at start of GH treatment could represent a negative factor since, as recently suggested by Thomas and Stanhope [7], the best

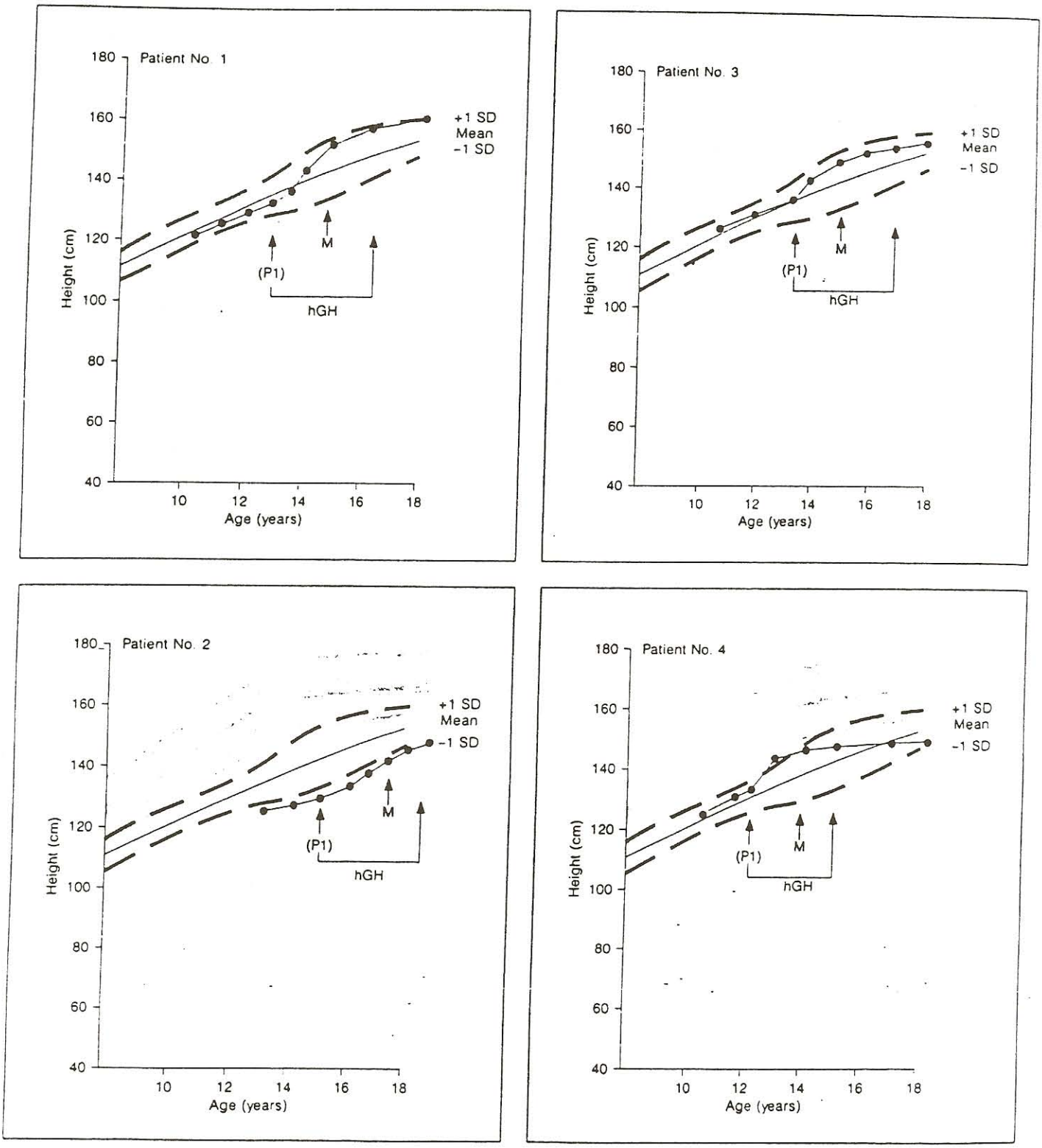

Fig. 1. Growth curves of the 4 girls with Noonan syndrome before and during GH treatment. The shaded area represents the normal population growth pattern according to Tanner. Growth curves (mean ± 1 SD) starting from 10 years are derived from those of Witt et al. [2]. P1 = Prepubertal stage according to Tanner standards; M = menarche.

results are likely to be obtained when GH treatment is started as early as possible. Furthermore, it is difficult to differentiate between the effect of puberty and that of GH treatment on height velocity. The more marked pubertal growth spurt in comparison to untreated patients, probably due at least in part to GH, might have allowed the treated ones to improve their final height. The unsuccessful outcome in patient 3 could be explained by the widely observed variability of response to treatment in nonconventional use of GH.

The results obtained in our small group of patients do not allow us to draw any final conclusion on the efficacy of GH treatment in Noonan syndrome. However, in our opinion it is advisable to consider GH treatment only when height is severely affected and cardiac pathology is not present or there is only a mild hemodynamic involvement. In the latter situation we recommend regular monitoring of cardiac status.

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