Response to Growth Hormone Treatment and Final Height in Noonan Syndrome in a Large Cohort of Patients in the KIGS Database

R. Raaijmakers¹, C. Noordam¹, G. Karagiannis², J.W. Gregory³, N.T. Hertel⁴, I. Sipilä⁵ and B.J. Otten¹

¹*Radboud University Nijmegen Medical Centre, Metabolic and Endocrine Disorders, Nijmegen, The Netherlands,* ²*Pfizer Endocrine Care, KIGS Medical Outcomes, Stockholm, Sweden,*

³*Wales College of Medicine, Cardiff University, Cardiff, Wales, UK,*

⁴*Odense University Hospital, Paediatric Department, Odense, Denmark and*

⁵*Children's Hospital, Department of Paediatric Endocrinology, Helsinki, Finland*

ABSTRACT

Background: Noonan syndrome (NS) is an autosomal dominant inherited disease, characterized by a distinctive facial appearance, congenital heart defects, and short stature. Treatment with growth hormone (GH) is an option to enhance height, but long-term effects are still unclear.

Patients and Methods: A cohort of 402 patients (269 males, 133 females), mean age 9.7 years at start with GH, was studied within the KIGS International growth database with respect to long-term response to GH therapy and final height after GH therapy.

Results: At the start of GH therapy median height was -2.61 SDS (Tanner 1966 standards). Seventy-three patients who were followed longitudinally for 3 years had an increment in height SDS (Ht SDS) over the first 3 successive years of 0.54, 0.13 and 0.13, respectively. Twenty-four patients had reached their final height after 4-12 years of GH treatment. Their Ht SDS increased from a median of -3.28 to a median of -2.41 at final height.

Conclusion: This group of patients with NS showed an early response to GH treatment, with an attenuation of this effect thereafter. At final height the median increment of final height was

0.61 SDS according to Tanner standards and 0.97 SDS according to Noonan standards. No serious side effects were reported.

KEY WORDS

Noonan syndrome, growth hormone, longitudinal growth, final height

INTRODUCTION

Noonan syndrome (NS) is a relatively common multiple congenital anomaly syndrome, first described in 1963 by Noonan and Emke¹, with an incidence of one per 1,000 live births^{2,3}. The inheritance of NS is autosomal dominant, with variability in expression. Sporadic mutations occur in 50% of patients. A gene was mapped on the long arm of chromosome 12 in 1994⁴. In 2001 the gene was identified as the *PTPN11* gene, accounting for approximately 50% of all cases⁵. Currently the diagnosis of NS remains mostly clinical. The main clinical features are characteristic facial features (hypertelorism, ptosis, down slanting palpebral fissures, low set posterior rotated ears and webbed neck), cardiac defects (most frequent pulmonary stenosis and hypertrophic cardiomyopathy; others are atrial septal defects, ventricular defects and coarctation of the aorta), chest deformity and growth retardation with short stature^{6,7}.

Fifty to 70% of patients with NS have short stature^{2,3,8}. Patients with NS have a typical growth pattern. Birth height and length are in the normal range, but patients fall below the 5th percentile at

Reprint address:

B.J. Otten

UMC St Radboud

Metabolic and endocrine disorders 833

P.O. Box 9101

6500 HB Nijmegen, The Netherlands

e-mail: b.otten@cukz.umcn.nl

approximately 3 months of age and remain growing below this percentile^{9,10}. Onset of puberty is delayed, and bone maturation shows an average delay of 2 years. Ranke *et al.* and Witt *et al.*^{9,10} recorded final heights from patients with NS. They reported mean heights of 162.5 and 161.0 cm in males and 152.7 and 150.5 cm in females, respectively. The underlying cause of short stature is unclear. Low insulin-like growth factor-I (IGF-I) levels have been reported^{11,12}, as well as impaired spontaneous growth hormone (GH) secretion¹¹⁻¹⁴. GH stimulation tests are reported as normal¹³.

Studies with GH for patients with NS have been conducted in relatively small patient groups and found an increase in height velocity in the short term, with a waning effect in the longer term¹⁵⁻¹⁷. Data on final height are scarce. The effect of GH treatment on long-term growth and final height in larger groups of patients needs to be assessed.

We performed a retrospective study in 402 patients with NS treated with GH, to evaluate the long-term effect and the gain in final height.

PATIENTS AND METHODS

All patients with a clinical diagnosis of NS who were enrolled in the KIGS International growth database from January 1985 until December 2004 were evaluated. Excluded were patients with insufficient reports on auxological details at the start of GH treatment. Auxological data (birth weight, birth height, height, height velocity, mid-parental height, weight, body mass index [BMI], GH dose and GH regimen), biochemical data (maximum growth hormone peak) and clinical data (age, sex, country of origin, pubertal stage, adverse events) were collected. The total cohort consisted of 402 patients (242 male, 118 female) from 27 countries. Sixty-three percent of the patients originated from Europe, 17% from North America, 9% from Australia and New Zealand, 1% from South America and 10% from Asia.

Out of the total database of 402 patients, two sub-cohorts were formed: one cohort with patients who had 3 years of prepubertal follow-up, and one cohort with patients who reached near adult height on GH treatment. Three years was the longest representative period of prepubertal follow-up in

this study group; after 3 years too many patients were lost to follow-up, mostly because of entering puberty.

Prepubertal follow-up was defined as yearly reports in patients without any signs of puberty. Puberty was defined as Tanner breast stage of at least 2 for girls¹⁸ and testis volume of at least 4 ml for boys. If there were no reports on pubertal markers, patients were considered to be in puberty if they had a chronological age of at least 10 years for girls and at least 12 years for boys.

Near adult height was defined as height velocity less than 2 cm per year, based on intervals of at least 9 months (with minimum age above 15.0 years for girls and 17.0 years for boys). Chronological age at start of GH treatment was below 14.0 years for females and 16.0 years for males. At least 1 year of prepubertal GH treatment was required, and at least 4 years of GH treatment in total.

Reference growth curves were used from Tanner and Whitehouse¹⁸ for children with normal growth and from Ranke *et al.*⁹ for children with NS.

Recombinant GH was given as daily subcutaneous injections, with a median dose of 0.24 mg/kg/week (range 0.17-0.77 mg/kg/week). Any adverse event occurring during GH treatment was reported by body system (musculo-skeletal, nervous, cardiovascular, respiratory, gastro-intestinal, metabolic and endocrine, hematological, urinary, reproductive and psychiatric).

Statistical analysis was by SAS and Windows XP Excel.

The study was reviewed and approved by an institutional ethics committee of the participating hospitals. Written informed consent was obtained from all patients and parents of patients involved in this study.

RESULTS

Baseline characteristics are shown in Table 1. Data from both sexes were pooled, since there were no significant differences between them.

Median birth weight and median birth length were -0.38 SDS and -0.69 SDS, respectively, according to Tanner standards. Mid-parental height was -0.41 SDS according to Tanner standards. The median maximal GH peak was 10 µg/l (measured

TABLE 1
Baseline characteristics of the total cohort of patients with Noonan syndrome

	n (total = 402)	Median	10th percentile	90th percentile
Gestational age (weeks)	375	40.00	36.00	41.00
Birth weight SDS	366	-0.38	-2.13	1.01
Birth length SDS	243	-0.69	-2.55	1.40
Midparental height SDS	368	-0.41	-2.09	1.28
Max. growth hormone peak (μg/l)	298	10.00	4.60	28.00

TABLE 2
Data at the start of growth hormone (GH) therapy of the total cohort of patients with Noonan syndrome

	n (total = 402)	Median	10th percentile	90th percentile
Chronological age (yr)	402	9.73	4.59	14.38
Bone age (yr)	109	7.30	2.25	11.90
Height SDS	402	-2.95	-4.29	-1.94
Height velocity (cm/yr)	182	4.39	2.89	6.45
Height - MPH SDS	368	-2.54	-4.53	-0.77
Weight SDS	402	-2.61	-4.13	-1.17
BMI SDS	402	-0.50	-1.87	1.00
Dose of GH (mg/kg/week)	402	0.24	0.16	0.36
Frequency of injections	402	7.00	6.00	7.00

MPH = mid-parental height; BMI = body mass index.

in 298 patients) and only a minority of patients had a stimulated GH value in the deficient range.

Data at start of GH treatment for all 402 patients are shown in Table 2.

Three year longitudinal prepubertal follow-up was available in 73 patients. Baseline characteristics and background data at the start of GH treatment and in the first and second year of follow-up were not statistically different from the total cohort. Median age at start was 7.73 years, median height was -2.86 SDS according to Tanner standards, and -1.04 SDS according to Noonan

standards, median weight was -2.20 SDS, with a median BMI of -0.62 SDS. Height velocity, height SDS and bone age advancement during three years of GH therapy are shown in Figures 1-3. Height velocity almost doubled in the first year, declined after 2 and 3 years, but remained approximately 1 cm/year higher after 3 years than at the start of treatment.

Height SDS increased by 0.76 SDS, with most gain during the first year and a smaller but constant gain during the second and third years of GH therapy. The increase according to Noonan stan-

Fig. 1: Height velocity during 3 years of growth hormone treatment in patients with Noonan syndrome.

Fig. 2: Height standard deviation score (Ht SDS) during 3 years of growth hormone treatment in patients with Noonan syndrome.

Fig. 3: Bone age advancement during 3 years of growth hormone treatment in patients with Noonan syndrome.

dards during the first, second and third year was 0.53, 0.22 and 0.15, respectively. The total increase in height SDS according to Noonan standards after 3 years was 0.81 SDS. Bone age increased from a median of 6.0 years at the start to a median of 9.3 years after 3 years of GH treatment.

Near adult height after at least four years of GH treatment was reached in 24 patients. Baseline characteristics and background data were not significantly different from the total cohort. Median age at start of GH treatment was 10.17 years, with a median height SDS of -3.24. Median duration of GH treatment was 7.59 years. The gain in height SDS per patient is shown in Figure 4. Median gain in height SDS according to Tanner standards was

Fig. 4: Height standard deviation score (Ht SDS) at start of growth hormone treatment (black bars) and at near adult height (white bars) in patients with Noonan syndrome.

0.61. Thirteen of the 24 patients (54%) had a final height below -2 SDS (Tanner standards), compared to 23 of the 24 patients (96%) at the start of GH treatment. Median gain in height SDS according to Noonan standards was 0.97 SDS. Bone age advanced from a median of 7.0 years (delay 3.17 years) to a median of 15.7 years (delay 2.74 years).

No serious adverse events in relation to GH treatment were observed.

One hundred and twenty eight patients discontinued GH treatment before reaching final height (31.8%). The main reasons mentioned are shown in Table 3. The group who discontinued treatment had a smaller response in height SDS after 1 year than the group that was treated for 3 years (mean 0.42 vs 0.53, median 0.42 versus 0.42), but this was not statistically significant.

DISCUSSION

This study provides an analysis of long-term GH treatment in a large group of patients with NS. There was a median gain in final height of 0.61 SDS according to Tanner standards and 0.97 SDS according to Noonan standards. Thus there was a significant but relatively small increase in final height. More than 50% of the patients reached a final height above -2 SDS (Tanner), whereas more than 95% of patients had a height below -2 SDS at the start of treatment. In our opinion, it is an important result in this lower height range for patients to achieve a final height above -2 SDS, within the socially accepted 'normal' range.

NS remains a clinical diagnosis, and thus making the correct diagnosis depends on the individual observer. The development of scoring systems^{8,19,20} partly solves this problem, but establishing the correct diagnosis remains a limitation in studies on patients with NS. However, we assume that the diagnosis was made correctly in our study, because it was made by experts on the basis of clinical characteristics. In addition, Turner's syndrome was excluded by chromosomal analysis.

The auxological data of our study group at birth were slightly below normal, which reflects the data reported in the literature, but the median height at start of treatment is in the lower height range for patients with NS. Presumably our study group

TABLE 3

Discontinued patients: reasons for discontinuation

Reason for discontinuation	n (total = 128)
Poor response	31
Parents' decision	10
Lost to follow up	10
Non-compliance	12
Normal height reached	6
Other	59

represents a pre-selection of short patients with NS, because these patients are more likely to be referred for GH treatment. The parents of the patients are also relatively short. This may partly reflect the fact that there would be some parents with NS, and the selection bias for GH treatment, which may reflect the inheritance of short stature due to other causes from the patients' parents.

There were more male patients than female patients in the study group. The male preponderance might reflect male preferential inheritance²¹, or less acceptance of short height in boys²². The drop-out proportion in this study was 31.8%. We observed a smaller response in the first year in the drop-out group compared to the long-term treatment group. Therefore, the long-term effect of GH we have reported may be a slight overestimation of the benefit of treatment for the total group.

Previous GH studies conducted in patients with NS are scarce and performed with relatively low numbers of patients. The gain in height SDS after treatment with GH is significant in the short term, but the observed effects are variable in the long term. De Schepper *et al.*¹⁵ treated 23 prepubertal patients with recombinant human GH at a dose of 0.35 mg/kg/week for 1 year. They found a mean increase in growth velocity of 4.0 cm/yr, and an increment in height SDS of 0.53, without acceleration of bone maturation. In patients treated with GH for 3 years, Noordam *et al.*¹⁷ found acceleration in bone maturation: 1.2 year/year versus 0.5 year per year in a control group. Gain in final height seemed to be compromised by this accelerating effect, with

a mean gain in height SDS corrected for bone age of only 0.3. The only larger study, performed by Kirk *et al.*¹⁶ in 66 patients, found a mean increment in height SDS of 0.6 in 3 years. In the ten patients in the study by Kirk *et al.* who reached near final height, the authors did not find a substantial improvement in final height, but duration of GH treatment was shorter compared to our study group (5.15 years versus 7.59 years). In the current study GH dosage was relatively low so the effect on final height would probably be better with a higher dosage, as used in the follow-up study by Noordam *et al.*¹⁷.

The benefits of GH treatment need to be measured against the burden of GH treatment. In our study no serious adverse events in relation to GH were reported. The reasons for discontinuation partly reflect the practical burden of GH treatment (non-compliance, problems with injections), as well as the high costs of GH treatment. The high costs of GH therapy have to be carefully counterbalanced against the gain in height. Lee *et al.* estimated the potential cost of GH therapy to be around 52,000 dollars per 2.54 cm of gain in height²². Although the estimate in that article was based on patients with idiopathic short stature, it gives an indication. The patients in the lower height range may benefit most from GH treatment, because with a relatively small gain in final height they still reach a socially more acceptable final height. The balance between the - significant but small - gain in height and the burden and costs of treatment needs to be considered in every patient.

CONCLUSIONS

In this study we found an early response to GH treatment with a waning effect thereafter. However, after 3 years of GH treatment there is still a gain in height SDS and at near adult height the gain was 0.61 SDS and 0.97 SDS, according to Tanner standards and Noonan standards, respectively. More than 50% of patients reached a final height above -2 SDS according to Tanner standards.

GH treatment is effective in NS without adverse side effects but the benefit and burden of treatment need to be considered when counselling patients about potential GH therapy in this condition.

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